IMAGING BRAIN NETWORKS IN FOCAL EPILEPSY: A PROSPECTIVE STUDY OF THE CLINICAL APPLICATION OF SIMULTANEOUS EEG-FMRI IN PRE-SURGICAL EVALUATION

Rachel Thornton MA, MBBS, MRCP

Department of Clinical and Experimental Epilepsy

Institute of Neurology

University College London (UCL)

Thesis submitted to UCL for the degree of Doctor of Philosophy, 2013
DECLARATION OF OWN WORK

I, Rachel Thornton confirm that the work presented here is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The scientific studies presented in this thesis reflect the contributions of a team of researchers including colleagues from the Department of Clinical and Experimental Epilepsy at the Institute of Neurology, UCL and the department of Clinical Neurophysiology at the Hopital de la Timone in Marseille in particular. However, this thesis only presents studies where I conducted most steps of data acquisition and analysis and the complete interpretation of the results following discussion with clinical colleagues and at supervision meetings. All the figures and illustrations are my own with the exception of two illustrations in the literature review, which have been referenced in the thesis.

Information derived from other sources has been indicated and referenced in this thesis.

I have outlined my own individual contribution to each of the studies published here and the contributions of my main co-workers and collaborators.
ABSTRACT

Epilepsy is a common disorder with significant associated morbidity and mortality. Despite advances in treatment, there remain a minority of people with pharmaco-resistant focal epilepsy for whom surgery may be beneficial. It has been suggested that not enough people are offered surgical treatment, partly owing to the fact that current non-invasive techniques do not always adequately identify the seizure onset zone so that invasive EEG is required. EEG-fMRI is an imaging technique, developed in the 1990s (Ives, Warach et al. 1993) which identifies regions of interictal epileptiform discharge associated haemodynamic changes, that are concordant with the seizure onset zone in some patients (Salek-Haddadi, Diehl et al. 2006). To date there has been no large scale prospective comparison with icEEG and postoperative outcome. This thesis presents a series of experiments, carried out in a cohort of patients scanned using EEG-fMRI as part of a multi-centre programme, designed to investigate the relationship between EEG-fMRI and intracranial EEG and to assess its potential role in pre-surgical evaluation of patients with focal epilepsy. The results suggested that positive, localised IED-related BOLD signal changes were sensitive for the seizure onset zone, as determined on icEEG, both in patients neocortical epilepsies, but were not predictive of outcome. Widespread regions of positive IED-related BOLD signal change were associated with widespread or multifocal abnormalities on icEEG and poor outcome. Patterns of haemodynamic change, identified using both data driven and EEG derived modeling approaches, correspond to regions of seizure onset on icEEG, but improvements for modeling seizures are required. A study of a single seizure in a patient who underwent simultaneous icEEG-fMRI, showed similar findings. An exploratory investigation of fMRI-DCM in EEG-fMRI, suggested it can provide information about seizure propagation and this opens new avenues for the non-invasive study of the epileptic network and interactions with function.
TABLE OF CONTENTS

i. List of figures ........................................................................................................................................ 18

ii. List of tables ......................................................................................................................................... 20

iii. List of Abbreviations ......................................................................................................................... 23

iv. Publications associated with this work .............................................................................................. 27

v. Acknowledgements ............................................................................................................................. 34

1 Outline and Statement of personal contribution .................................................................................... 36

2 Literature review ..................................................................................................................................... 39

  2.1 Epidemiology ..................................................................................................................................... 40

  2.2 Classification of Epilepsy Syndromes ............................................................................................... 40

  2.3 Focal Epilepsy .................................................................................................................................... 42

  2.4 Aetiology of Focal Epilepsy .............................................................................................................. 46

  2.5 Management of Focal Epilepsies ....................................................................................................... 46

      2.5.1 Pharmacological ......................................................................................................................... 46

      2.5.2 Pharmacoresistant epilepsy ..................................................................................................... 47

  2.6 Surgical Treatment of Epilepsy .......................................................................................................... 48

      2.6.1 Resective Surgery: .................................................................................................................... 48

      2.6.2 Pre-surgical Evaluation ............................................................................................................ 48

      2.6.3 Epilepsy surgery in Specific Syndromes ................................................................................... 50
2.6.4 General Complications of Epilepsy Surgery ........................................ 54
2.6.5 Surgical resection for epilepsy in patients with ‘normal MRI’ ............... 55
2.6.6 Palliative procedures ........................................................................... 55
2.6.7 Radiosurgery ......................................................................................... 56
2.6.8 Outcome Measures in Epilepsy Surgery .............................................. 57
2.6.9 Outcome following Resective Surgery ................................................. 59

2.7 Magnetic Resonance Imaging ................................................................. 62
2.7.1 History of MRI ..................................................................................... 62
2.7.2 Physics of nuclear magnetic resonance imaging (NMR) ....................... 62
2.7.3 Measuring the signal ........................................................................... 63
2.7.4 Relaxation Times: ............................................................................. 64
2.7.5 Structural MRI in Epilepsy ................................................................. 66
2.7.6 Magnetic Resonance Spectroscopy ..................................................... 71
2.7.7 Diffusion Tensor Imaging ................................................................... 72
2.7.8 Diffusion tensor imaging in Epilepsy .................................................. 73

2.8 The role of additional non-invasive techniques in localising focal epilepsy .... 75
2.8.1 Radionucleide imaging ....................................................................... 75
2.8.2 PET ........................................................................................................ 76
2.8.3 Ictal SPECT .......................................................................................... 79
2.9 EEG and epileptogenesis

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9.1</td>
<td>Physiological mechanisms of epileptogenesis</td>
<td>80</td>
</tr>
<tr>
<td>2.9.2</td>
<td>Initiation and propagation of the interictal spike</td>
<td>82</td>
</tr>
<tr>
<td>2.9.3</td>
<td>Role of Excitatory synaptic transmission</td>
<td>82</td>
</tr>
<tr>
<td>2.9.4</td>
<td>Role of inhibitory Activity</td>
<td>83</td>
</tr>
<tr>
<td>2.9.5</td>
<td>The basis of the EEG signal</td>
<td>83</td>
</tr>
<tr>
<td>2.9.6</td>
<td>Recording EEG</td>
<td>85</td>
</tr>
<tr>
<td>2.9.7</td>
<td>Normal EEG</td>
<td>86</td>
</tr>
<tr>
<td>2.9.8</td>
<td>The Routine (interictal) EEG in Epilepsy</td>
<td>87</td>
</tr>
<tr>
<td>2.9.9</td>
<td>Ictal Scalp EEG in Epilepsy</td>
<td>90</td>
</tr>
</tbody>
</table>

2.10 Magnetoencephalography and Magnetic source imaging (MSI)

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.10.1</td>
<td>Comparison with EEG</td>
<td>94</td>
</tr>
<tr>
<td>2.10.2</td>
<td>Validation of MEG/ magnetic source imaging (MSI)</td>
<td>95</td>
</tr>
</tbody>
</table>

2.11 Intracranial EEG recording

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11.1</td>
<td>Advantages of icEEG</td>
<td>96</td>
</tr>
<tr>
<td>2.11.2</td>
<td>Methods of recording icEEG</td>
<td>97</td>
</tr>
<tr>
<td>2.11.3</td>
<td>Limitations of Intracranial EEG</td>
<td>101</td>
</tr>
<tr>
<td>2.11.4</td>
<td>Complications</td>
<td>103</td>
</tr>
<tr>
<td>2.11.5</td>
<td>Comparison with Non-invasive Methods of Localisation</td>
<td>103</td>
</tr>
</tbody>
</table>
2.11.6 Clinical Interpretation of icEEG................................................................. 104

2.12 Functional MRI: Basic concepts and application in Epilepsy .................. 107

2.12.1 The Nature of BOLD contrast................................................................. 107

2.12.2 Properties of the BOLD signal................................................................. 108

2.12.3 Spatial Resolution of BOLD signal ......................................................... 108

2.12.4 Temporal Resolution .................................................................................. 109

2.12.5 Neural basis of the BOLD response.......................................................... 109

2.12.6 Neurovascular coupling: the basis of the BOLD signal ....................... 110

2.12.7 Measuring and Interpreting BOLD Signal Change: principles of fMRI experiments ................................................................................................................. 111

2.12.8 fMRI applied to Epilepsy .......................................................................... 112

2.12.9 Memory fMRI ............................................................................................ 115

2.13 EEG fMRI ..................................................................................................... 118

2.13.1 Approach to simultaneous EEG-fMRI recording: Technical aspects ...... 119

2.13.2 Technical considerations ............................................................................ 119

2.13.3 Summary: technical aspects ...................................................................... 128

2.13.4 EEG-fMRI applied to Epilepsy .................................................................. 128

2.13.5 Evolving analysis methodology: interictal data ........................................ 144

2.13.6 Ictal EEG-fMRI .......................................................................................... 145
2.13.7  Modelling approaches to ictal data .......................................................... 147

2.13.8  Applications of data driven approaches to fMRI in Epilepsy .................... 153

2.13.9  ICA in EEG-fMRI. .................................................................................. 153

2.13.10 ICA of EEG in EEG-fMRI studies ......................................................... 155

2.13.11 Application of ICA in this work .............................................................. 156

2.14  Moving away from the ‘zone concept’: Measures of Connectivity in Focal Epilepsy and their application in EEG-fMRI .......................................................... 156

2.14.1  Functional Specialization and Functional Integration ............................... 158

2.14.2  Functional Connectivity (FC): ................................................................. 159

2.14.3  Applications of functional connectivity analysis to understanding epileptic networks ............................................................................................................ 160

2.14.4  Measures of Causality .............................................................................. 161

2.14.5  Granger Causality .................................................................................... 162

2.14.6  Dynamic Causal Modelling ...................................................................... 162

2.14.7  Other measures of causality in epilepsy .................................................... 165

2.14.8  Generalised Epilepsies ............................................................................. 165

2.14.9  Summary: connectivity ............................................................................. 166

3  NEW EXPERIMENTS: COMMON METHODOLOGY ........................................ 167

3.1.1  Recruitment ............................................................................................... 167
3.1.2 Exclusions ................................................................. 167
3.1.3 Clinical course ............................................................. 168
3.1.4 EEG-fMRI Acquisition ....................................................... 169
3.1.5 EEG pre-processing ......................................................... 170
3.1.6 fMRI pre-processing ....................................................... 170
3.1.7 General Linear Model Analysis of IED-related BOLD signal change .... 171
3.1.8 Comparison with Post-operative Imaging ............................... 173
3.1.9 Comparison of fMRI patterns with Intracranial EEG: Interictal Data ........ 173
3.1.10 Ictal Group .................................................................. 175

4 RESULTS: ........................................................................... 176

4.1 Details of patients .............................................................. 176

5 Experiment 1: Pilot study comparing IED related BOLD signal change with
post-operative outcome ................................................................ 180

5.1 Summary .......................................................................... 180

5.2 Introduction: ...................................................................... 181

5.3 Methods ........................................................................... 183

5.3.1 Patients ......................................................................... 183

5.3.2 Clinical course ............................................................... 183

5.3.3 EEG-fMRI acquisition .................................................... 184
5.3.4  fMRI processing and analysis........................................................................ 184
5.3.5  Postoperative imaging.................................................................................. 185
5.3.6  Results.......................................................................................................... 186
5.3.7  Case reports................................................................................................ 189
5.4  Discussion........................................................................................................ 195
  5.4.1  Methodological Considerations ................................................................. 195
  5.4.2  Clinical Significance.................................................................................... 198
  5.4.3  Deactivations.............................................................................................. 200
  5.4.4  Non-resected group..................................................................................... 200
  5.4.5  Further Work.............................................................................................. 201
5.5  Conclusion........................................................................................................ 201

6  Experiment 2: EEG-fMRI reveals epileptic networks and is a useful adjunct to
pre-surgical evaluation in Focal Cortical Dysplasia............................................. 203
  6.1  Summary: ...................................................................................................... 203
  6.2  Introduction................................................................................................... 205
  6.3  Materials and methods.................................................................................. 207
    6.3.1  Patients................................................................................................. 207
    6.3.2  Electroclinical evaluation ...................................................................... 207
    6.3.3  EEG-fMRI Acquisition......................................................................... 208
6.4 Results ........................................................................................................................................... 210

6.4.1 EEG-fMRI Results ......................................................................................................................... 210

6.4.2 Relationship of BOLD signal change to resection and outcome ........................................... 218

6.4.3 IED-correlated BOLD decreases ................................................................................................. 218

6.4.4 Patients with no IEDs during EEG-fMRI ...................................................................................... 218

6.4.5 Representative cases ..................................................................................................................... 219

6.5 Discussion ......................................................................................................................................... 225

6.5.1 Main findings of this experiment ................................................................................................. 225

6.5.2 Neurophysiological significance ................................................................................................. 226

6.5.3 Clinical Significance ....................................................................................................................... 228

6.5.4 Methodological Considerations .................................................................................................... 231

6.5.5 CONCLUSIONS ............................................................................................................................ 233

7 Experiment 3: Exploring Haemodynamic changes linked to seizures using
EEG-fMRI: Comparison with of General Linear Model, Independent Component
Analysis and intracranial EEG ............................................................................................................. 234

7.1 Summary: ......................................................................................................................................... 234

7.2 Introduction: ....................................................................................................................................... 235

7.3 Materials and Methods: .................................................................................................................... 237

7.3.1 Patients Selection ........................................................................................................................... 237
7.3.2 EEG pre-processing and event identification: ........................................... 238

7.3.3 fMRI pre-processing: ............................................................................. 238

7.3.4 General Linear Model Analysis............................................................... 239

7.3.5 Classification of independent components............................................. 241

7.3.6 Comparison of the GLM results with intracranial data.......................... 242

7.3.7 Independent component analysis (ICA) ............................................... 243

7.3.8 Correlation of GLM with IC time courses............................................. 246

7.4 Results ........................................................................................................ 246

7.4.1 General Linear Model ............................................................................ 248

7.4.2 Case Reports............................................................................................ 253

7.5 Discussion .................................................................................................. 265

7.5.1 Summary of findings .............................................................................. 265

7.5.2 Methodological considerations .............................................................. 267

7.5.3 Significance of results ............................................................................ 275

7.5.4 Further Work: Implications for this study ............................................ 280

7.5.5 Conclusion............................................................................................... 280

8 Experiment 4: What can EEG-fMRI tell us about the dynamics of the epileptic network? A study comparing Dynamic Causal Modeling for fMRI with intracranial EEG........................................................................................................... 282
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.5.1</td>
<td>Main findings:</td>
<td>307</td>
</tr>
<tr>
<td>8.5.2</td>
<td>Neurophysiological Significance:</td>
<td>308</td>
</tr>
<tr>
<td>8.5.3</td>
<td>Methodological and Physiological Considerations</td>
<td>310</td>
</tr>
<tr>
<td>8.5.4</td>
<td>Comparison with existing studies:</td>
<td>314</td>
</tr>
<tr>
<td>8.5.5</td>
<td>Clinical significance</td>
<td>315</td>
</tr>
<tr>
<td>8.5.6</td>
<td>Future directions</td>
<td>316</td>
</tr>
<tr>
<td>8.6</td>
<td>Conclusion:</td>
<td>317</td>
</tr>
<tr>
<td>9</td>
<td>Experiment 5: Intracranial EEG-fMRI reveals changes in the epileptic network associated with sub-clinical seizures.</td>
<td>318</td>
</tr>
<tr>
<td>9.1</td>
<td>Summary</td>
<td>318</td>
</tr>
<tr>
<td>9.2</td>
<td>Introduction</td>
<td>319</td>
</tr>
<tr>
<td>9.3</td>
<td>Methods:</td>
<td>321</td>
</tr>
<tr>
<td>9.3.1</td>
<td>Patient selection:</td>
<td>321</td>
</tr>
<tr>
<td>9.3.2</td>
<td>Scalp EEG-fMRI:</td>
<td>321</td>
</tr>
<tr>
<td>9.3.3</td>
<td>icEEG-fMRI Acquisition:</td>
<td>322</td>
</tr>
<tr>
<td>9.3.4</td>
<td>Preprocessing and labeling of events:</td>
<td>323</td>
</tr>
<tr>
<td>9.3.5</td>
<td>Analysis:</td>
<td>323</td>
</tr>
<tr>
<td>9.4</td>
<td>Results:</td>
<td>324</td>
</tr>
<tr>
<td>9.4.1</td>
<td>Clinical details:</td>
<td>324</td>
</tr>
</tbody>
</table>
10.3.6 Post-operative outcome............................................................... 340

10.4 Results......................................................................................... 341

10.4.1 Patient groups ........................................................................ 341

10.4.2 Type and number of IEDs ............................................................ 341

10.4.3 Analysis of patients who had IEDs during recording: comparison with icEEG 342

10.4.4 Analysis of all patients: relationship between EEG-fMRI and icEEG ...... 345

10.4.5 Relationship with post-operative outcome at 3 years .................... 347

10.4.6 Patients with no IEDs ................................................................. 348

10.5 Discussion .................................................................................... 348

10.5.1 Main findings ............................................................................ 348

10.5.2 Clinical and neurophysiological Significance .................................. 349

10.5.3 Methodological considerations; .................................................. 352

10.6 Conclusions ................................................................................ 353

11 Conclusions and Context ................................................................. 354

11.1 Summary of main findings ............................................................ 354

11.1.1 EEG-fMRI and post operative outcome ....................................... 354

11.1.2 Non-invasive imaging of epileptic networks in Focal Cortical Dysplasia . 355

11.1.3 Haemodynamic changes linked to seizures .................................... 355
11.1.4 Electrophysiological networks involved in the generation of seizures: A validation of Dynamic Causal Modeling with intracranial EEG .............................................. 355

11.1.5 Simultaneous intracranial EEG-fMRI of ictal activity ........................................ 356

11.1.6 Medium term follow up ......................................................................................... 356

11.2 Methodological considerations ................................................................................. 357

11.2.1 The problem of yield: Approaches to improve sensitivity .................................. 357

11.2.2 Improving specificity: Refinement of approaches to modeling ......................... 358

11.3 Neurobiological and Clinical Context: Future Directions ...................................... 359

11.3.1 Ictal EEG-fMRI: Understanding what happens before the seizure ............. 359

11.3.2 From Zones to Networks: using connectivity to inform interpretation of EEG-fMRI 361

11.3.3 Translation to surgical planning: What is the role of EEG-fMRI? ............. 362

12 Appendix A: Consent form ......................................................................................... 364

13 Bibliography ..................................................................................................................... 365
I. LIST OF FIGURES

Figure 2-1: Typical layout of scalp EEG electrodes .......................................................... 85

Figure 2-2 Typical Haemodynamic response function ....................................................... 111

Figure 2-3 Set up for EEG-fMRI experiments at the Epilepsy Society MRI Unit, ........ 121

Figure 3-1: Example of typical General Linear Model showing effects of interest and relevant regressors modelled ................................................................. 172

Figure 5-1: EEG-fMRI and post-operative MRI in patient 1.............................................. 189

Figure 5-2: EEG-fMRI and post-operative MRI in patient 5............................................. 191

Figure 5-3 EEG-fMRI results and post-operative MRI in patient 10......................... 194

Figure 6-1 EEG-fMRI results compared with icEEG .......................................................... 221

Figure 6-2 Example of icEEG implantation and recording .............................................. 222

Figure 6-3 Example of icEEG implantation and recording ............................................. 223

Figure 6-4 Patient 22, ..................................................................................................... 224

Figure 7-1 Patient 1, Ictal series....................................................................................... 255

Figure 7-2: Case 6, Ictal series. ....................................................................................... 261

Figure 8-1: Examples of models with bidirectional coupling for a 3 node network.... 290

Figure 8-2: Example of the models specified for DCM..................................................... 292

Figure 8-3 Typical evolution of a seizure on icEEG. ........................................................ 295
Figure 8-4 Patient 1: IED-related GLM result in SPM8 overlaid on fused T1 weighted MRI with CT with electrodes in situ. ................................................................. 299

Figure 8-5 Example of model specification and posterior probability of each model. 300

Figure 8-6: Example of identified sets of coactivated structures. .......................... 303

Figure 8-7 Screenshot showing example of calculation of directionality index from icEEG ........................................................................................................... 304

Figure 8-8 Results of comparison second DCM approach ........................................... 306

Figure 9-1 T1-weighted MRI with intracranial electrodes in situ .................................. 325

Figure 9-2 Typical intracranial EEG recording showing interictal discharges from right and left hippocampi and amygdale ......................................................... 326

Figure 9-3 Typical clinical seizure arising from the left hippocampus. Arrow indicates fast, low amplitude activity at onset ................................................................. 327

Figure 9-4. Example of typical sub-clinical seizure arising from the right amygdala.. 327

Figure 9-5 Results of Scalp EEG-fMRI ................................................................. 328

Figure 9-6 Seizure related BOLD signal change recorded with icEEG-fMRI ................. 330

Figure 10-1 Chart showing the relationship between patients with localising EEG-fMRI and post-operative outcome. (number of patients on y-axis) ......................... 347
II. LIST OF TABLES

Table 2.1 ILAE classification of focal epilepsies.................................................. 43

Table 2.2 ILAE classification of seizure syndromes........................................... 44

Table 2.3 Definition of cerebral regions involved in seizures defined by intracranial EEG ......................................................................................................................... 50

Table 2.4 Engel classification of Outcome following surgical resection for focal epilepsy(Engel J 1993) ........................................................................................................... 58

Table 2.5 ILAE measures of outcome with respect to seizure frequency following surgery for focal epilepsy........................................................................................................ 59

Table 2.6 Recommended MRI sequences for Focal cortical dysplasia................. 69

Table 2.7 Ictal EEG findings in various generalised epilepsy syndromes ............. 92

Table 2.8 Summary of the results of EEG-fMRI studies comparing BOLD signal change with electroclinical localisation of seizures ................................................. 131

Table 4.1 Timeline of experimental work related to developments in methodology... 178

Table 5.1 Electroclinical data for pilot study............................................................. 187

Table 6.1 Clinical details of patients with a diagnosis of Focal Cortical Dysplasia at one year post-operative follow up................................................................. 211

Table 6.2 Results of IED-related BOLD signal change, icEEG and post-operative outcome...................................................................................................................... 213

Table 6.3 Details of intracranial EEG ...................................................................... 215

Table 7.1 Electroclinical details of patients who had seizures during scanning....... 247
Table 7.2 Results of General Linear Model Analysis of ictal data ........................................... 251
Table 7.3 Results of Independent Component Analysis .............................................................. 252
Table 7.4 Concordance of ictal EEG-fMRI and icEEG ................................................................. 252
Table 7.5 Correlation of fMRI GLM with time course of the respective 'ictal' independent component .................................................................................................................. 253
Table 8.1 Electroclinical details of patients included in DCM analysis .................................. 297
Table 8.2 Results of IED-related GLM and fMRI DCM analysis ................................................. 301
Table 9.1 Table showing the locations of each depth electrode. Electrode contacts are labelled 1-6, mesial to lateral. Electrode contacts are referred to in later figures by the same labels. ......................................................................................................................... 325
Table 9.2 IED related BOLD signal change recorded during icEEG-fMRI .......................... 329
Table 9.3 BOLD signal change associated with electrographic seizures arising from the right amygdala in icEEG-fMRI .......................................................................................... 329
Table 10.1 Numbers of patients who underwent EEG-fMRI. .................................................... 341
Table 10.2 Summary of findings ................................................................................................. 342
Table 10.3 Table showing the numbers of patients with localising or non-localising EEG-fMRI and icEEG studies (patients with IEDs during EEG-fMRI) ........................ 344
Table 10.4 Predictive value of localized IED-related BOLD signal change on EEG-fMRI for a single icEEG focus ........................................................................................................... 345
Table 10.5 Relationship between localised EEG-fMRI and localised icEEG (figures indicate numbers of patients in each group) ................................................................. 346
Table 10.6 Specificity/ sensitivity of EEG-fMRI in all patients for single focus on icEEG (including those with no IEDs on EEG-fMRI) ........................................... 346

Table 10.7: Relationship between extent of EEG-fMRI and post-operative outcome in patients with IEDs (3 years post-operative follow up)............................................. 348
## III. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>AED</td>
<td>Anti-epileptic drug</td>
</tr>
<tr>
<td>ATLR</td>
<td>Anterior temporal lobe resection</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood oxygen level dependent signal</td>
</tr>
<tr>
<td>CAE</td>
<td>Childhood absence epilepsy</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CMRO$_2$</td>
<td>Cerebral metabolic rate of oxygen</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CPS</td>
<td>Complex Partial Seizure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebro-spinal Fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed Tomography Angiogram</td>
</tr>
<tr>
<td>DCM</td>
<td>Dynamic Causal modelling</td>
</tr>
<tr>
<td>dHb</td>
<td>De-oxy haemoglobin</td>
</tr>
<tr>
<td>DMN</td>
<td>Default mode network</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxy-ribonucleic Acid</td>
</tr>
<tr>
<td>DNMT</td>
<td>Dysembyronic neuroepithelial tumour</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion weighted Imaging</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EEG-fMRI</td>
<td>Simultaneous Electroencephalography and functional magnetic resonance imaging</td>
</tr>
<tr>
<td>EEG-MREG</td>
<td>Simultaneous Electroencephalography and Magnetic resonance encephalography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrical source imaging</td>
</tr>
<tr>
<td>ExTLE</td>
<td>Extra-temporal lobe epilepsy</td>
</tr>
<tr>
<td>EZ</td>
<td>Epileptic Zone</td>
</tr>
<tr>
<td>FCD</td>
<td>Focal Cortical Dysplasia</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FLE</td>
<td>Frontal Lobe Epilepsy</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid Attenuated Inversion Recovery</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width at half maximum</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma amino butyric acid</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamate</td>
</tr>
<tr>
<td>GE</td>
<td>General Electric</td>
</tr>
<tr>
<td>GLM</td>
<td>General linear model</td>
</tr>
<tr>
<td>GM</td>
<td>Grey Matter</td>
</tr>
<tr>
<td>GSW</td>
<td>Generalised spike and wave discharge</td>
</tr>
<tr>
<td>GTCS</td>
<td>Generalised Tonic Clonic Seizure</td>
</tr>
<tr>
<td>HA</td>
<td>Hippocampal Atrophy</td>
</tr>
<tr>
<td>HS</td>
<td>Hippocampal Sclerosis</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
</tr>
<tr>
<td>icEEG</td>
<td>Intracranial Electroencephalography</td>
</tr>
<tr>
<td>IGE</td>
<td>Idiopathic generalised Epilepsy</td>
</tr>
<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>IED</td>
<td>Interictal Epileptiform Discharge (on scalp EEG)</td>
</tr>
<tr>
<td>IS</td>
<td>Interictal spike (on intracranial EEG)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>IZ</td>
<td>Irritative Zone</td>
</tr>
<tr>
<td>JAE</td>
<td>Juvenile Absence Epilepsy</td>
</tr>
<tr>
<td>JME</td>
<td>Juvenile Myoclonic Epilepsy</td>
</tr>
<tr>
<td>LFP</td>
<td>Local field potential</td>
</tr>
<tr>
<td>LZ</td>
<td>Lesional Zone</td>
</tr>
<tr>
<td>MCD</td>
<td>Malformation of Cortical Development</td>
</tr>
<tr>
<td>MEG</td>
<td>Magneto-encephalography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MRS</td>
<td>Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>mTLE</td>
<td>Mesial Temporal Lobe Epilepsy</td>
</tr>
<tr>
<td>MUA</td>
<td>Multi-unit activity</td>
</tr>
<tr>
<td>NAA</td>
<td>N-Acetyl Aspartate</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
</tr>
<tr>
<td>OLE</td>
<td>Occipital Lobe Epilepsy</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal component analysis</td>
</tr>
<tr>
<td>PDS</td>
<td>Paroxysmal depolarizing shift</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PLE</td>
<td>Parietal Lobe Epilepsy</td>
</tr>
<tr>
<td>PMG</td>
<td>Polymicrogyria</td>
</tr>
<tr>
<td>PNH</td>
<td>Periventricular nodular heterotopia</td>
</tr>
<tr>
<td>RF</td>
<td>Resonance frequency</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RSN</td>
<td>Resting state network</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SHZ</td>
<td>Schizencephaly</td>
</tr>
<tr>
<td>SISCOM</td>
<td>Subtraction ictal SPECT (Single Photon Emission Computed Tomography)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>coregistered to MRI</td>
<td></td>
</tr>
<tr>
<td>sICA</td>
<td>Spatial independent component analysis</td>
</tr>
<tr>
<td>SNH</td>
<td>Sub-cortical nodular heterotopia</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
</tr>
<tr>
<td>SOZ</td>
<td>Seizure Onset Zone</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>SPM</td>
<td>Statistical Parametric Mapping</td>
</tr>
<tr>
<td>SPS</td>
<td>Simple Partial Seizure</td>
</tr>
<tr>
<td>TCA</td>
<td>Temporal clustering analysis</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>tICA</td>
<td>Temporal independent component analysis</td>
</tr>
<tr>
<td>TLE</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel based morphometry</td>
</tr>
<tr>
<td>VOI</td>
<td>Voxel of interest</td>
</tr>
</tbody>
</table>
IV. PUBLICATIONS ASSOCIATED WITH THIS WORK

Material from chapter 2 (introduction and literature review) as well as the experiments presented in chapters 5-7 has been published as book chapters or in peer reviewed journals as first author.


Chapter 7: *Imaging haemodynamic changes related to seizures: comparison of EEG-based general linear model, independent component analysis of fMRI and intracranial*

In addition, I undertook further work in collaboration with colleagues at the Epilepsy Society and Institute of Neurology as well as further afield during the period of study, acting as co-author on the following publications.

**Papers in Peer-reviewed Journals:**


**Personal contribution:** Participation in scanning and EEG-fMRI analysis of patients, participation in preparation of the manuscript

*Improving the sensitivity of EEG-fMRI studies of epileptic activity by modelling eye blinks, swallowing and other video-EEG detected physiological confounds.*


**Personal contribution:** Participation in scanning and EEG-fMRI analysis of patients, participation in preparation of the manuscript

*With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging.* Grouiller F,

Personal contribution: Recruitment, scanning and EEG-fMRI analysis of patients (which overlapped with experiments presented here), interpretation of intracranial EEG data, major role in experimental design and preparation of the manuscript


Personal contribution: Recruitment, scanning and EEG-fMRI analysis of patients (which overlapped with experiments presented here), major role in experimental design and preparation of the manuscript


Personal contribution: Assistance with designing and preparing phantom set up to optimize replication of clinical conditions, scanning and participation in preparation of the manuscript

Causal hierarchy within the thalamo-cortical network in spike and wave discharges.


Personal contribution: Participated in recruitment and scanning of patients, participation in preparation of the manuscript

Personal contribution: Recruitment, scanning and EEG-fMRI analysis of patients, collection and interpretation of clinical data, participation in preparation of the manuscript

Continuous EEG source imaging enhances analysis of EEG-fMRI in focal epilepsy.


Personal contribution: Recruitment, scanning and EEG-fMRI analysis of patients, collection and interpretation of clinical data, participation in preparation of the manuscript

In addition the following abstracts related to this work were presented at Conferences as poster sessions or platform sessions:

A. C. Coan, U. J. Chaudhary, B. M. Campos, S. Perani, R. Thornton, S.


Vulliemoz S, Rodionov R, Carmichael D, Thornton R, Guye M, Spinelli L, Michel C, Duncan J, Lemieux L; Continuous EEG Source imaging enhances EEG-fMRI analysis, Annual Meeting of the Swiss Society for Neurosciences, Lausanne, Switzerland, March 2010

Vulliemoz S, Rodionov R, Carmichael D, Thornton R, Guye M, Spinelli L, Michel C, Duncan J, Lemieux L; Continuous EEG Source imaging enhances EEG-fMRI analysis, Alpine Brain Imaging Meeting, Champéry, Switzerland Jan. 2010


Vulliemoz S, Thornton R, Rodionov R, Carmichael D, Guye M, Spinelli L, Michel C, Lemieux L; The epileptic networks in space and time: simultaneous electric source imaging and EEG-fMRI; UK chapter of the International League against Epilepsy, Dundee, UK, July 2008

Thornton R, Comparison of ictal and interictal EEG-fMRI in focal Epilepsy, Platform Presentation, Joint meeting Association of British Neurologists and British Society for Clinical Neurophysiology, Dublin, March 2008

V. ACKNOWLEDGEMENTS

I am extremely grateful to a huge number of people who have supported me in completing this thesis. The work presented here would not have been possible without the inspiration and support of my two supervisors, Professors John Duncan and Louis Lemieux. I am extremely grateful for your wise words, patience, encouragement, reviews of endless drafts and friendship. My colleagues in the EEG-fMRI group, Serge Vulliemoz, Helmut Laufs, Roman Rodionov, and David Carmichael taught me a huge amount and have helped and supported me so much over the last few years. I am also grateful for the scientific input and friendship from my ‘fellow fellows’ at the Epilepsy Society MRI Unit; Silvia Bonelli, Mahinda Yogarajah, Umair Chaudhary, Christian Vollmar, Maria Centeno, Anna Vaudano, Jason Stretton, Nils Focke and Gavin Winston. Philippa Bartlett, Jane Burdett and Elaine Williams spent a lot of time, not only producing excellent scans, but also encouraging me whether things were going well or badly! Peter Gilford has been endlessly patient with my IT glitches.

I am grateful to Professor Matthew Walker, Dr Shelagh Smith, Mr Andrew McEvoy, Dr Beate Diehl and Catherine Scott at the National Hospital for Neurology and Neurosurgery for their guidance and to Dr Robert Elwes and Professor Mark Richardson at Kings College Hospital and Dr Samden Lhatoo at Frenchay Hospital for their enthusiastic support of the project. I am particularly thankful to the Clinical Neurophysiology team at the Hopital de la Timone in Marseille, especially Professors Patrick Chauvel, Fabrice Bartolomei and Maxime Guye, for making me so welcome in their department, despite my halting French, and for teaching me so much about epilepsy and intracranial EEG. Thanks also to Drs Aileen McGonigal and Sandrine Aubert for help with EEG interpretation and obtaining imaging data in the patients from Marseille.
Sajitha Cannadathu helped with the data acquisition. Fabrice Wendling and Jean Daunizeau both gave valuable advice for the DCM section and there are many other people who have given me suggestions and listened to my ideas. Particular thanks also go to all the patients who participated in the study and their families and friends who came with them.

My parents, Hilary and Paul, have always encouraged me to pursue my ambitions and I would not have got to this point without their support. I am also extremely thankful to both them and Anne and Geoff for providing practical support in food and childcare format while I was writing up. Finally, thank you to Anna, Joseph and Madeleine and especially to Greg for keeping me going - without your love and support, I would never have finished.
1 OUTLINE AND STATEMENT OF PERSONAL CONTRIBUTION

The aim of this thesis was to evaluate the role of EEG-fMRI in presurgical evaluation, by comparison of IED-related haemodynamic changes with icEEG and post-operative outcome. Over the course of the experimental work, there were developments in recording and analysis of EEG-fMRI data and I also investigated haemodynamic changes related to ictal activity and the use of dynamic causal modeling applied to EEG-fMRI data. Towards the end of the period of study, the first successful recordings of icEEG-fMRI in humans were undertaken by our group and the findings in one of the first three patients is also reported here.

Chapter 2 is a literature review which details background information concerning the clinical diagnosis, investigation and treatment of epilepsy with particular reference to the pre-surgical evaluation of focal epilepsy and the various approaches to recording and interpreting scalp and intracranial EEG. The later parts of this chapter comprise a brief review of advanced imaging techniques, with particular focus on the historical and recent development and application of EEG-fMRI and a brief review of the methods used to study connectivity in focal epilepsy.

Chapter 3 details common methodology used in the experimental work presented in chapters 5-10 and is referred to as appropriate. It does not include methodology specific to each individual experiment, which is described separately in the relevant chapter.

Chapter 4 introduces the sections detailing results and discussion.

Chapter 5 describes my initial pilot study undertaken comparing the results of EEG-fMRI with post-operative outcome at 12 months. I was able to show that when the region of brain underlying areas of IED-related BOLD signal change was entirely resected, patients had a good post-operative outcome with respect to seizures at 12
months, and that in patients where regions of IED-related BOLD signal change lay outside the resection margin, outcomes were less favourable.

**Personal Contribution:** I was responsible for the recruitment, data acquisition and analysis for all patients at 3T as well as follow up data for the purposes of the experiment in all patients. A Salek-Hadaddi did the scanning at 1.5 T (3 patients), which I analysed. I was primarily responsible for the design of the experiment in conjunction with my supervisors.

In **Chapter 6**, I compared IED-related BOLD signal change with post-operative outcome and icEEG in all patients in the cohort with a diagnosis of focal cortical dysplasia. I was able to demonstrate that regions of IED-related BOLD signal change are often concordant with the irritative and seizure onset zones on icEEG and that where regions of BOLD signal change are widespread, the epileptic network is often more widespread or multifocal.

In **Chapter 7**, I undertook an exploratory analysis of ictal related haemodynamic change in all the patients in the cohort who has seizures during scanning. I was able to show that a physiologically informed EEG based general linear model, was successful in identifying patterns of BOLD signal change specific to seizures and colocalised with the seizure onset zone in patients in whom scalp EEG was an accurate representation of seizures. I also showed that applying a data driven technique (independent component analysis) to the fMRI data revealed patterns of haemodynamic change colocalised with the seizure onset zone on icEEG in patients with focal seizures.

**Personal contribution:** The data presented in chapters 6 and 7 were taken from a cohort of 99 patients recruited and scanned as part of a multicenter MRC funded programme investigating the use of EEG-fMRI in patients with focal epilepsy. As the Clinical Fellow on this programme, I was responsible for coordinating the recruitment
and scanning of most of the patients over a three year period as well as the collection and interpretation of the clinical data including the icEEG and post-operative follow up data. I was responsible for much of the EEG-fMRI data acquisition in collaboration with S Vulliemoz, H Laufs and S Cannadathu. I was primarily involved in the study design for both experiments in conjunction with my supervisors and Roman Rodionov (Chapter 7) and carried out all the data analysis and interpretation of results myself.

In **Chapter 8** I undertook a validation study of dynamic causal modeling in fMRI (fMRI-DCM) data. I was able to demonstrate that one could infer directionality in the epileptic network using fMRI-DCM, and the results matched those obtained using lag correlation analysis of interictal spikes on icEEG and also patterns of seizure propagation within the network on icEEG. The methodology for this is currently evolving very quickly and the work presented will provide the basis for improved and refined analysis of fMRI-DCM in epilepsy in the future.

**Personal Contribution:** The patient group presented here overlaps with the group presented in chapter 6. I was primarily involved in the study design in conjunction with Prof Louis Lemieux, M Guye and F Bartolomei. I was responsible for the analysis of both the EEG-fMRI and icEEG data in this group.

**Chapter 9** is a case report of a patient who had an electrographic seizure while undergoing simultaneous icEEG-fMRI. This is a novel technique, which was pioneered by our research group during the course of this work and in this patient patterns of BOLD signal change specifically associated with seizure onset recorded on icEEG were demonstrated. To my knowledge this is a unique data set.

**Personal Contribution:** I was responsible for the recruitment, monitoring and icEEG interpretation for this patient as well as post processing and data analysis. I was
involved in the study design in collaboration with D Carmichael, S Vulliemoz, R Rodionov and L Lemieux.

A summary of the entire patient cohort is presented in Chapter 10 along with an evaluation of the potential clinical role of EEG-fMRI. The study is the first prospective, systematic comparison of EEG-fMRI with icEEG and post-operative data and is the only study, to our knowledge, which evaluates the technique in an unselected group, which was not limited to patients with frequent IEDs. I have demonstrated that in patients with IEDs during scanning, the identification of localized IED-related BOLD signal change is both a sensitive and specific marker for a localized SOZ on icEEG. The results also confirm, however, that for standard IED-related GLM analysis of EEG-fMRI data, the technique has very low sensitivity unless patients have frequent IEDs and that novel approaches to EEG analysis are needed to improve this.

**Personal Contribution:** The patient group includes patients presented in chapters 6 and 7 and forms the entire cohort of patients from the MRC programme described above. I was primarily involved in the design of this study and undertook much of the data acquisition (as described above) and all of the analysis related to the work in this chapter.

I interpreted icEEG in all patients, but the assessment of icEEG findings was also discussed with each patient’s clinical team in all cases.

## 2 LITERATURE REVIEW

The following literature review begins with a summary of the background to the project. Sections 2.1-2.10 summarize the pertinent features of epilepsy as a disease and standard techniques in the evaluation and surgical treatment of patients with focal epilepsy including structural and advanced MRI, scalp EEG as well as briefly reviewing
the contributions of MEG and radionuclide imaging to pre-surgical evaluation.

Section 2.11-2.14 focuses on the specific techniques used in the experimental work including intracranial EEG (2.11), fMRI applied to epilepsy (2.12), EEG-fMRI (2.13) and approaches to studying functional networks in epilepsy (2.14).

2.1 Epidemiology

Epilepsy is a significant cause of morbidity and mortality with a worldwide incidence of 100 per 100,000 per year falling to 50 per 100,000 specifically in developed countries with a range of 40-70/100,000 per year (Forsgren, Beghi et al. 2005, Forsgren, Hauser et al. 2005). In developing countries, the incidence is estimated at 100-190/100,000 per year, and it is thought that social deprivation plays a significant role in this increased figure (Heaney, MacDonald et al. 2002). Recent figures from the UK support this hypothesis that social deprivation may be an independent risk factor for developing epilepsy. It affects people of all ages and carries an increased risk of mortality, with community-based studies reporting a SMR of 2-3 times (Forsgren, Hauser et al. 2005) higher than the general population, rising to five times the general population for pharmacoresistant epilepsy (Téllez-Zenteno, Ronquillo et al. 2010) and 500 deaths per year in the UK alone. It is a heterogeneous disorder encompassing a wide range of syndromes and seizure types and has many causes.

2.2 Classification of Epilepsy Syndromes

A consensus opinion on the classification of Epilepsy has been historically difficult to achieve as there is variability in the preferred approach (for example one may choose to classify by seizure type, aetiology or syndrome). In reality, a clinically useful classification needs to take both seizure type and syndrome into account and an ILAE (International League Against Epilepsy) commissioning group has proposed a
classification scheme, which considers syndrome, aetiology, seizure type and semiology (Wieser, Blume et al. 2001), based on a consensus in 1981 and updated in 2010 (Berg, Berkovic et al. 2010).

Epilepsy syndromes can be divided into generalised and partial or focal, contrasting the diffuse nature of the former with seizures arising from one region of the brain in the latter. The classification continues to evolve, however; patients with focal epilepsy do not always have a single site of seizure onset, but may have a widespread region from which seizures arise, or multiple foci and there is evidence from animal models in particular that some epilepsies traditionally classified as generalised may, in some cases have underlying focal neurophysiological abnormalities (e.g. focal pre-frontal abnormalities in animal models of absence epilepsies). In addition, as will be discussed at various points in the thesis, the concept of focal epilepsy as a disease of brain networks rather than a single region is now a widely held view (Spencer 2002).

The rapidly developing field of clinical genetics has increasingly identified genetic susceptibility for epilepsy leading to refinement of the classification of epilepsies described as ‘genetic’ (incorporating many of those previously considered ‘idiopathic’).

The patients in this study were recruited from 2006-2010, and so I have used the 2001 version (which updates the 1989 version) throughout this work to ensure consistency. The classification in 2001 attempted to define epilepsy according to 5 different diagnostic axes.

Axis 1: Ictal phenomenology - from the Glossary of Descriptive Ictal Terminology can be used to describe ictal events with any degree of detail needed.

Axis 2: Seizure type - from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.

Axis 3: Syndrome - from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
Axis 4: Aetiology - from a Classification of Diseases Frequently Associated with Epileptic Seizures or epilepsy syndromes when possible, genetic defects, or specific pathological substrates for symptomatic focal epilepsies.

Axis 5: Impairment - this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the WHO ICIDH-2.

2.3 Focal Epilepsy

This work is concerned with patients with focal epilepsy, specifically those have epilepsy which may be amenable to surgical intervention. As its name suggests, focal epilepsy has its onset localised to a particular brain region, although which brain region this is varies from patient to patient and may not always be easily identifiable by conventional means. Focal epilepsy refers to the group of epilepsy syndromes defined by the presence of partial seizures implying a focal onset. This is a heterogeneous group of disorders, both in terms of aetiology and clinical semiology and is classified according to the ILAE classification as follows (Table 2.1 describes semiology, Table 2.2, syndrome).

Note: In the 1989 (updated in 2001) classification of epilepsy, the discriminators ‘idiopathic’ (unknown cause), ‘symptomatic ’ (with an underlying structural or metabolic cause) and ‘cryptogenic’ (unidentified cause) were used to separate seizure syndromes. In the 2010 classification these were updated to ‘genetic’ (where a genetic cause is known). There are also various changes to the descriptions of seizure semiology (simple partial seizures are now referred to as ‘focal seizures without impairment of consciousness’ (with subjective sensory (previously aura) or observable motor components) and ‘complex partial seizures’ as ‘focal seizures with impairment of consciousness or ‘dyscognitive seizures’).
Table 2.1 ILAE classification of focal epilepsies

<table>
<thead>
<tr>
<th>Focal sensory seizures</th>
<th>With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)</td>
</tr>
<tr>
<td>Focal motor seizures</td>
<td>With elementary clonic motor signs</td>
</tr>
<tr>
<td></td>
<td>With asymmetric tonic motor seizures (e.g., supplementary motor seizures)</td>
</tr>
<tr>
<td></td>
<td>With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)</td>
</tr>
<tr>
<td></td>
<td>With hyperkinetic automatisms</td>
</tr>
<tr>
<td></td>
<td>With focal negative myoclonus</td>
</tr>
<tr>
<td></td>
<td>With inhibitory motor seizures</td>
</tr>
<tr>
<td></td>
<td>Gelastic seizures</td>
</tr>
<tr>
<td></td>
<td>Hemiclonic seizures</td>
</tr>
<tr>
<td><strong>Secondarily generalized seizures</strong></td>
<td></td>
</tr>
<tr>
<td>Continuous seizure types</td>
<td>Generalized status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Focal status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Epilepsia partialis continua of Kojevnikov</td>
</tr>
<tr>
<td></td>
<td>Aura continua</td>
</tr>
<tr>
<td></td>
<td>Limbic status epilepticus (psychomotor status)</td>
</tr>
<tr>
<td></td>
<td>Hemiconvulsive status with hemiparesis</td>
</tr>
<tr>
<td><strong>Reflex seizures in focal epilepsy syndromes</strong></td>
<td>Visual stimuli</td>
</tr>
<tr>
<td></td>
<td>Patterns or flickering lights</td>
</tr>
<tr>
<td></td>
<td>Other visual stimuli</td>
</tr>
<tr>
<td></td>
<td>Thinking</td>
</tr>
<tr>
<td></td>
<td>Music</td>
</tr>
</tbody>
</table>

*taken from the 2001 ILAE taskforce on classification of the epilepsies.*
<table>
<thead>
<tr>
<th>Eating</th>
<th>Praxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatosensory</td>
<td>Proprioceptive</td>
</tr>
<tr>
<td>Reading</td>
<td>Startle</td>
</tr>
<tr>
<td>Hot water</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.2 ILAE classification of seizure syndromes**

<table>
<thead>
<tr>
<th>Childhood onset epilepsy syndromes</th>
<th>Benign familial neonatal seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Early myoclonic encephalopathy</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Ohtahara syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Migrating partial seizures of infancy</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>West syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Benign myoclonic epilepsy in infancy</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Benign familial infantile seizures</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Benign infantile seizures (non-familial)</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Dravet's syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>HHE syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Myoclonic status in non-progressive encephalopathies</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Early onset benign childhood occipital epilepsy (Panayiotopoulos type)</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Late onset childhood occipital epilepsy (Gastaut type)</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Lennox–Gastaut syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Landau–Kleffner syndrome</td>
</tr>
<tr>
<td>Childhood onset epilepsy syndromes</td>
<td>Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)</td>
</tr>
</tbody>
</table>

*taken from the 2001 ILAE taskforce on classification of the epilepsies.*
<table>
<thead>
<tr>
<th><strong>Familial Epilepsies</strong></th>
<th>Autosomal dominant nocturnal frontal lobe epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Familial temporal lobe epilepsies</td>
</tr>
<tr>
<td></td>
<td>Generalized epilepsies with febrile seizures plus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Reflex epilepsies</strong></th>
<th>Idiopathic photosensitive occipital lobe epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary reading epilepsy</td>
</tr>
<tr>
<td></td>
<td>Startle epilepsy</td>
</tr>
<tr>
<td></td>
<td>Other visual sensitive epilepsies</td>
</tr>
</tbody>
</table>

| **Symptomatic (or probably symptomatic) focal epilepsies** | |
|-----------------------------------------------------------|
| **1. Limbic epilepsies** | Mesial temporal lobe epilepsy with hippocampal sclerosis |
|                            | Mesial temporal lobe epilepsy defined by specific aetiologies |
|                            | Other types defined by location and etiology         |
| **2. Neocortical epilepsies** | Rasmussen syndrome                                   |
|                            | Other types defined by location and aetiology         |

*taken from the 2001 ILAE taskforce on classification of the epilepsies.*
2.4 Aetiology of Focal Epilepsy

As previously discussed the aetiology of most focal epilepsy is multi-factorial.

- **Congenital**: There is genetic susceptibility to epilepsy and several specific syndromes for which gene defects have been identified (e.g. Ring chromosome 20, tuberous sclerosis). In other syndromes it is clear there is some inherited tendency to seizures although a specific gene defect has not been identified. Abnormalities of brain development may give rise to focal seizures either owing to underlying genetic abnormalities or related to metabolic or vascular insults in utero or during the neonatal period and include malformations of cortical developments, developmental tumours, gliosis as well as other rare defects. The genetics of focal epilepsy is complex and evolving, but the details are outside the scope of this work and will not be discussed further.

- **Acquired**: Focal epilepsy can result from regional brain abnormalities arising from infection, trauma, malignancy or any other cause.

2.5 Management of Focal Epilepsies

2.5.1 Pharmacological

Anti-epileptic drugs (AEDs) are the first line choice in the management of focal seizures. A successful pharmacological treatment is aimed at reducing the frequency and eventually aborting seizures with no or tolerable side effects. Bromide salts were the first AED to be used in the 1800s, and it was not until the use of Phenobarbital started in 1912, that there were other therapeutic options. Randomised control trials of
AEDs show that drug treatment is effective even after a single unprovoked seizure, in reducing the risk of seizure recurrence, although the introduction of AEDs depends on the likelihood of seizure recurrence and is generally not commenced until an individual has had more than one seizure. In adults with a diagnosis of epilepsy, 47% will become seizure free with tolerable side effects on the first AED tried (Kwan and Brodie 2000) while 20-30% of those who are not seizure free will become so with a second drug (Kwan and Brodie 2000) (Schiller and Najjar 2008). Following the failure of two AEDs at increased doses, the likelihood of seizure freedom with a third or subsequent AED is much lower. 60-80% of people with epilepsy now achieve control through pharmacological means.

The exact mechanism of anti-convulsant medication varies depending on the drug, but the final effect usually results in direct or indirect action on sodium channels. The rate at which an axon fires is determined in part by the rate at which a sodium channel in the membrane can close following membrane depolarization (this determines the ‘refractory period’ during which an axon cannot fire. Binding of anti-convulsants to the voltage gated sodium channels prolongs the ‘open phase’ preventing further persistent depolarization which reflects epileptiform activity. Other anti-convulsant drugs act on inhibitory pathways mediated by GABA (gamma amino butyric acid) and glutamate (perampanel).

2.5.2 Pharmacoresistant epilepsy

Pharmacoresistance is defined as failure to achieve seizure freedom following adequate trials of at least two appropriate AEDs (Kwan, Arzimanoglou et al. 2010) (based on the evidence that 60-80% of patients will become seizure free following this as outlined above). If this occurs, surgical intervention is often considered, either
resection with curative intent or a palliative procedure. If surgical intervention is not appropriate there is some evidence for other interventions such as trial of a ketogenic diet. Detailed discussion of these measures is beyond the scope of this work.

2.6 Surgical Treatment of Epilepsy

The approaches to the treatment of focal epilepsy by surgical means may divided into those aimed at cure (resective surgery) and palliative procedures. The range of Palliative procedures includes resection, but also includes ‘functional resections’ (e.g. corpus callosotomy, in essence a functional hemispherectomy) as well as functional procedures such as deep brain stimulation or vagal nerve stimulation.

2.6.1 Resective Surgery:

Successful surgical resection is possible in focal epilepsy, provided that the seizure onset zone (SOZ), defined as the region from which seizures arise, can be identified and also that it can be removed while sparing functionally important regions (e.g. language or motor cortex). Around 3% of patients who have epilepsy are thought to be suitable for investigation for epilepsy surgery (Duncan 2010) and approximately half that number are likely to be suitable for resection (Lhatoo, Solomon et al. 2003). At present, in the United Kingdom, this figure is not reached (Epilepsy 2007).

2.6.2 Pre-surgical Evaluation

The epileptogenic zone (EZ) was first identified in (grossly) structurally normal cortex in the 19th century by MacEwan and HughlingsJackson (Woolf 2010). Following this, in the early 20th century, small numbers of patients underwent surgery for epilepsy, usually associated with underlying structural abnormalities. The development of
cerebral angiography and EEG, which first showed the association of interictal spikes with seizures in patients with both absence epilepsy and temporal lobe epilepsy in the 1930s allowed refinement of the surgical approach (Gibbs 1935) and much more recently the development of magnetic resonance imaging has allowed identification of structural lesions giving rise to seizures.

Although the methods of evaluation and resection have become increasingly advanced, successful surgical resection continues to rely on the pre-operative demonstration of a single region which gives rise to seizures and does not overlap with eloquent cortex (Rosenow and Luders 2001). Resective operations may involve the removal of a radiologically identified structural lesion (lesionectomy), removal of radiologically normal epileptogenic cortex (corticectomy) or complete or partial lobectomy. Identification of the target region for resection may often be achieved with non-invasive techniques, such that an individual would normally undergo scalp EEG, detailed structural imaging, and EEG-video telemetry to determine the precise seizure onset zone as well as neuro-psychological assessment and functional imaging or intracarotid amytal injection to determine the likely impact on function (this particularly applies to language and memory function in temporal lobe epilepsy). Additional techniques such as radionuclear imaging, high density scalp EEG and magnetoencephalography may add more information regarding the location of the irritative and seizure onset zones. Improved structural MRI using higher fields has increased the sensitivity for the detection of anatomical abnormalities.

The gold standard method for seizure onset localization however, remains intracranial EEG (icEEG), using depth electrodes inserted into the brain, sub-dural electrode grid arrays placed on the cortical surface or a combination of the two, and this continues to
be required in a minority of patients to localize the region from which seizures arise and is discussed in section 2.11.

A number of definitions, used in this thesis, which describe the various brain regions involved in the generation of seizures and defined on icEEG are useful in determining resection type and extent (Rosenow and Luders 2001).

**Table 2.3 Definition of cerebral regions involved in seizures defined by intracranial EEG**

<table>
<thead>
<tr>
<th>Region</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritative Zone (IZ)</td>
<td>Area giving rise to interictal epileptiform activity (spikes)</td>
</tr>
<tr>
<td>Epileptogenic Zone (EZ)</td>
<td>Area which, if resected, results in seizure freedom</td>
</tr>
<tr>
<td>Lesional Zone (LZ)</td>
<td>Area of anatomical abnormality</td>
</tr>
<tr>
<td>Functional deficit Zone</td>
<td>Area which, if resected, results in a specific functional deficit (e.g. loss of motor function or language impairment)</td>
</tr>
<tr>
<td>Seizure onset Zone (SOZ)</td>
<td>Area from which seizures arise</td>
</tr>
</tbody>
</table>

**2.6.3 Epilepsy surgery in Specific Syndromes**

**2.6.3.1 Surgery for temporal lobe epilepsy**

The most common curative surgical procedure in epilepsy is anterior temporal lobe resection in which good outcomes with regard to seizure freedom are consistently reported, particularly in patients who have total resection of regions of hippocampal sclerosis (70% seizure free at 2 years, 69% at 15 years) (Wiebe, Blume et al. 2001),
Seizure freedom rates are lower in cases where there are bilateral abnormalities on EEG, other co-existing pathology (for example focal cortical dysplasia (FCD)) or normal MRI. In a large long term follow up study, published last year, outcomes at 10 years were found to be less favourable, but the authors noted that if a patient is seizure free at 2 years, they have a very high chance of achieving long term seizure freedom, while early seizure recurrence was predictive of poor long term outcome (de Tisi, Bell et al. 2011).

Specific neurological complications of anterior temporal lobe resection, in addition to the general complications of neurosurgery, most commonly include specific language and/or memory impairment (Spencer and Huh 2008) or varying degrees of visual field defect (homonymous superior quadrantanopia) owing to lesions of Meyer’s loop (Yogarajah, Focke et al. 2009, Winston, Yogarajah et al. 2011, Winston, Daga et al. 2012) at the time of surgery (Katz, Awad et al. 1989, Hughes, Abou-Khalil et al. 1999). The severity of the field defect appears to correlate with the length of the resection.

Factors which predict verbal episodic memory impairment include age (poorer outcome after age 50), neuropsychometric measures including pre-operative verbal IQ and pre-existing memory deficit (in dominant ATLR, the individuals with higher verbal IQ and no pre-existing verbal memory deficit have poorer outcome with respect to verbal memory compared with those who have a pre-existing deficit or low verbal IQ (Sherman, Wiebe et al. 2011)), age of onset of epilepsy, presence of cortical dysplasia, the extent of resection and both seizure and non-seizure outcome following surgery (Baxendale, Thompson et al. 2006). Conversely contralateral memory function impairment prior to surgery (i.e. non-verbal memory impairment in dominant anterior temporal lobe resection) is predictive of amnesia.
There has been much interest in the prediction of post-operative language and memory decline, in particular the development of non-invasive alternatives to the intracarotid-amytal test (Wada test) which was traditionally used to lateralize language function, but has now been superseded in many centres by the use of language fMRI and the clinical use of memory fMRI to predict post- ATL R memory decline is also a realistic possibility (Richardson, Strange et al. 2004) (Bonelli, Powell et al. 2010) and is discussed further below.

Neuro-psychiatric complications specific to temporal lobe resection include depression and anxiety as well as psycho-social complications related to changes in seizure patterns. Increased rates of post-operative depression and anxiety were originally thought to be more prevalent following right temporal lobe resection, but evidence suggests that laterality does not affect this. Factors which increase the likelihood of psychiatric complications include pre-existing psychiatric illness and poor response to epilepsy surgery with respect to seizures (Tellez-Zenteno, Patten et al. 2007). Interestingly, post-operative seizure freedom is associated with improved quality of life measures even in the context of cognitive decline (Langfitt, Westerveld et al. 2007).

2.6.3.2 Surgical resection in Malformations of Cortical Development

Neocortical resection is by its nature, more variable than mesial temporal lobe resection. The development of advanced MRI sequences as well as other non-invasive methods of presurgical assessment has resulted in improved detection of the severe type 2 focal cortical dysplasia (recently reclassified by the ILAE (Blümcke, Thom et al. 2011)) in particular, but successful surgery relies on the complete resection of the lesion without impact on function. In FCD, there may be overlap between the lesional, epileptogenic and irritative zones, but they do not necessarily coincide
completely. In consequence, iEEG recordings are usually required to delineate the lesional, irritative and epileptogenic zones (Sisodiya, Fauser et al. 2009).

Complications specific to neocortical resection are essentially dependent on the area of cortex to be resected and specifically the physiological function underlying the resected cortex (e.g. resection complicated by haemorrhage within primary motor cortex leading to motor deficit). Other complications relate to the relatively long term implantation of EEG electrodes and seizure recurrence or the development of a new seizure syndrome owing to limited resection; the chief predictor of good outcome in FCD remains the complete resection of the region of seizure onset (Krsek, Maton et al. 2009), while resection of any cortex giving rise to seizures is also associated with seizure freedom.

Other malformations of cortical development (polymicrogyria, schizencephaly, hemimegencephaly etc) may be improved by surgery when the abnormality is restricted to one region or even hemisphere and cortical resection is sometimes attempted in these situations, particularly in paediatric practice. Extensive invasive EEG is required to delineate the epileptogenic zone, as the irritative zone is often extensive and may involve regions outside (often contralateral to) the EZ.

In periventricular nodular heterotopia (PNH), surgical outcome appears to relate to the extent of the lesion –small series of patients with unilateral PNH have been reported to have good outcome (Luders and Schuele 2006). One group has demonstrated that selective amygdalo-hippocampectomy may be of benefit in patients with associated PNH even without resecting the PNH itself (Aghakhani, Kinay et al. 2005), suggesting that the PNH is not necessarily intrinsically epileptogenic in these cases. In contrast, sub-cortical nodular heterotopia (SNH), usually has intrinsically epileptogenic cortex
overlying it which requires complete resection for seizure freedom, such that good surgical outcome is restricted to those patients with a unilateral lesion (Tassi, Colombo et al. 2005). In addition, in patients with bilateral subcortical band heteroropia, surgical treatment (including both resection and palliative procedures such as multiple subpial transection or functional hemispherectomy) is unhelpful, even if a localized area of cortex appears to give rise to seizures (Bernasconi, Martinez et al. 2001). There is increasing data on long term outcome following resection for malformations of cortical development suggesting that outcome is dependent on complete resection of the structural abnormality and size of lesion as well as local icEEG abnormalities only. A recent study of 143 patients suggested seizure freedom rates of 65% at 5 years and 67% at 10 years in patients with focal cortical dysplasia and a visible lesion on MRI (Chang, Wang et al. 2011).

One of the potential roles of advanced neuroimaging techniques in the future, including resting state fMRI may be to improve understanding of the relationship between malformations of cortical development and underlying structures and the methods for doing this are explored in this thesis.

2.6.4 General Complications of Epilepsy Surgery

Mortality rates for epilepsy surgery are quoted at between 0.5 and 1%, with reported causes of death including cerebral haemorrhage, infection and seizures (late deaths) in addition to complications of anaesthesia. The mortality rates vary widely between types of resection, for example, a recent population based study in the USA reported no mortality with anterior temporal lobe resection (ATLR for unilateral TLE with hippocampal sclerosis) (Elsharkawy, May et al. 2009) while higher rates are reported
with surgery for extensive extra-temporal resections or arterio-venous malformations (AVMs) (Engel J 1993). Of note, long term mortality rates for patients with focal epilepsy who undergo surgery are lower than for those who do not (Bell, Sinha et al. 2010). Meta-analyses suggest the major complication rate (cerebral haemorrhage, infection and stroke) is around 5% (Tellez-Zenteno, Dhar et al. 2007).

2.6.5 Surgical resection for epilepsy in patients with ‘normal MRI’

Despite advances in imaging (both MRI and other modalities), there remain a significant fraction of patients with focal epilepsy and normal MRI, 40-73% of whom have been shown subsequently to have cortical dysplasia (Chapman, Wyllie et al. 2005, Lee, Lee et al. 2005). In these cases, iEEG is often required to delineate the epileptogenic, irritative and functional deficit zones, but some studies report that the rate of seizure freedom is comparable with patients who have an evident lesion MRI (Lee, Lee et al. 2005, McGonigal, Bartolomei et al. 2007). It should be noted, however, that these studies are not standardized in terms of the quality of MRI used, and are considered ‘MRI negative’ at relatively low field strength using conventional sequences. Advances in MRI may challenge these findings and are discussed further in sections 2.7.5-2.7.7.

2.6.6 Palliative procedures

Complete seizure control may not be a realistic objective in every patient, but useful palliation can still be gained in patients who have disabling seizures with both respective approaches and more recently, electrical stimulation.
2.6.6.1 Electrical stimulators

Vagal nerve stimulation, using a subcutaneous simulator, has been an established therapy for many years. Early studies suggested seizure reduction rates of 50-75% at one year, and longer term outcome studies reported that VNS insertion for focal seizures achieves an average reduction in seizures of around 55% (DeGiorgio, Schachter et al. 2000, Elliott, Morsi et al. 2011, Fisher 2012). Seizure freedom, however, is rare and the rate is probably comparable only with a 3rd or subsequent anti-convulsant drug. A disadvantage of VNS insertion is the presence of intra-corporeal metal leads which may limit imaging if surgery is considered in the future (although high field structural MRI at 3T has been shown to be safe (Gorny, Bernstein et al. 2010).

Deep brain stimulation, well established in the treatment of movement disorders, has also been used to treat refractory epilepsy. Long term follow up on a large scale is not yet available and the technique continues to evolve. Targets used for stimulation in focal epilepsy include the hippocampi, sub-thalamic nucleus and the centro-median thalamic nucleus (Romanelli, Striano et al. 2012).

2.6.6.2 Disconnection

‘Functional resection’ (e.g. Corpus callosotomy or functional hemispherectomy) involving disruption of white matter tracts may be of value in severe epilepsy, although such approaches are not often curative

2.6.7 Radiosurgery

Sterotactic radiosurgery can be used for small lesions localized in regions where conventional surgery is likely to prove more difficult. Its use is most established in the
treatment of hypothalamic hamartoma, cavernomas and mesial TLE (Régis, Rey et al. 2004). The efficacy of this is not fully evaluated as the technique is relatively novel and the technique takes a prolonged period (1-2 years) to take effect often following an initial increase in seizure frequency at 6-8 months (Quigg M 2008). Outcome studies suggest a decrease in seizure frequency in patients treated with radiosurgery, but low rates of seizure freedom (Quigg, Rolston et al. 2012).

2.6.8 Outcome Measures in Epilepsy Surgery

Success in Epilepsy surgery is generally measured by assessing the rate of seizure freedom in the short, medium and long term, as well as Quality of life measures (subjective and objective). Seizure freedom scales are of particular relevance to this work as they provide an objective means of evaluating the utility of any pre-surgical evaluation technique. There are two rating scaled for the assessment of seizure frequency following surgery in general use

The Engel classification, introduced in 1993, divides outcomes into 4 broad categories at a single point in time.
Table 2.4 Engel classification of Outcome following surgical resection for focal epilepsy (Engel J 1993)

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Seizure free or no more than a few early non-disabling seizures; or seizures on drug-withdrawal only</td>
</tr>
<tr>
<td>II</td>
<td>Disabling seizures occur rarely during a period of at least 2 years; disabling seizures may have been frequent soon after surgery; nocturnal seizures</td>
</tr>
<tr>
<td>III</td>
<td>Worthwhile improvement; seizure reduction for prolonged periods but less than two years</td>
</tr>
<tr>
<td>IV</td>
<td>No worthwhile improvement; some reduction, or worsening are possible</td>
</tr>
</tbody>
</table>

It has become increasingly apparent that the Engel Classification, however, does not allow a longitudinal assessment of the success of surgery as the outcome measures do not allow for change over time. In addition, early seizures may have some independent relationship with long term outcome and the system does not allow a precise quantification of seizure frequency.

In 2001, the International League Against Epilepsy proposed a new classification system and suggested a yearly appraisal of seizure outcome, allowing longitudinal assessment of surgical success and useful data to be gleaned for long term follow up studies. The system also has the advantage of being quantifiable, allowing inter-centre comparison.
<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Completely seizure free</td>
</tr>
<tr>
<td>1b</td>
<td>Completely seizure free since surgery, no auras</td>
</tr>
<tr>
<td>2</td>
<td>Only aura, no other seizures</td>
</tr>
<tr>
<td>3</td>
<td>One to 3 seizure days per year; may have auras</td>
</tr>
<tr>
<td>4</td>
<td>Four seizure days per year or up to a 50% reduction in seizures from baseline</td>
</tr>
<tr>
<td>5</td>
<td>Less than a 50% reduction in seizure days from baseline, or an increase in seizure days of up to 100% from baseline</td>
</tr>
<tr>
<td>6</td>
<td>Increase in number of seizure days from baseline of more than 100%</td>
</tr>
</tbody>
</table>

This classification was updated in 2010, but the above classification, current at the time data acquisition commenced for this thesis, will be used in this work.

### 2.6.9 Outcome following Resective Surgery

Seizure freedom rates following surgery vary depending on a number of independent prognostic factors including pathophysiology, presence and extent of abnormalities on structural imaging and the location (at a lobar level) of the seizure onset zone.
(including potential overlap with specific functional regions of the brain e.g. primary
motor cortex or speech areas). As mentioned above, the best outcomes are achieved
when a single region of seizure onset is identified away from eloquent cortex.

There have been attempts to study outcomes of epilepsy surgery in the medium term,
and it is consistently reported that the most successful group at 5 years following
surgery were those with unilateral mesial TLE (41-79% seizure free (Wiebe, Blume et
al. 2001)) compared with neocortical resection (36-76% seizure freedom reported, but
this is not classified by lobe). In focal cortical dysplasia, outcomes are less favourable
and the main independent predictor of seizure freedom is the complete resection of the
epileptogenic an irritative zones as seen on intracranial EEG which is often required to
adequately localize seizure onset (Krsek, Maton et al. 2009). Patients who have
multiple foci of cortical dysplasia also have worse outcomes (Fauser, Schulze-Bonhage
et al. 2004).

More recently comprehensive long term outcome studies have begun to emerge. De
Tisi et al have reported the experience of one centre over 10 years and showed
seizure freedom rates of 52% at 5 years and 47% at 10 years across all patients
(including those who remained on at least one medication), while reiterating the
findings of previous studies that the best outcomes were in those with mesial temporal
lobe epilepsy. In addition they also reported that relapse became less likely with longer
periods of remission, while remission was much less likely if there was long period in
which seizures were refractory to treatment following surgery. In common with other
studies of post-operative surgical outcome, there was a decline in seizure freedom with
longer follow up periods.
Multiple studies have attempted to characterize factors which influence the likelihood of seizure freedom in epilepsy. In temporal lobe epilepsy a meta-analysis has demonstrated ictal dystonia (presumably a reflection of rapid seizure propagation) had a negative predictive value in the short term while long term outcome was influenced by the duration of epilepsy prior to surgery (Janszky, Janszky et al. 2005). Other independent predictive factors of a favourable outcome include unilateral discharges on EEG and the presence of hippocampal sclerosis rather than other lesions (Elsharkawy, May et al. 2009).

2.6.9.1 Non-seizure outcomes

Although seizure freedom is the most obvious parameter by which to measure the success of epilepsy surgery, there are other important factors, which have been investigated. In patients who undergo mesial temporal lobe epilepsy in particular, measures of cognitive outcome remain are particularly relevant as the resection often impacts on language and memory function. Resection within the occipital and frontal cortices may also result in functional deficit, particularly when the SOZ is close to primary motor or visual cortex.

There have been several studies which have evaluated psychiatric outcome following surgery for epilepsy, given the common psychiatric complications of neurosurgery, but also that psychiatric co-morbidities are significantly more common in people with epilepsy compared with the general population (Tellez-Zenteno, Dhar et al. 2007), with a particular increase in schizophrenia and related disorders. One study has noted that mood and anxiety disorders were especially common after surgery and recent evidence suggests that the primary independent predictor of post-surgical psychiatric morbidity is seizure control (Spencer and Huh 2008).
Independent studies which assess the outcome of surgery in relation to quality of life measures which are not discussed in detail here, but have been reviewed comprehensively elsewhere (Seiam, Dhaliwal et al. 2011).

2.7 Magnetic Resonance Imaging

High quality structural MRI remains the imaging technique of choice for identifying structural abnormalities giving rise to epilepsy and structural abnormalities are found in 74% of people with focal epilepsy referred to tertiary referral centres (Duncan 2010). The technique has developed over the latter half of the twentieth century and new scanners and sequences have allowed increased sensitivity and specificity as well as the evolution of new techniques for assessing areas of abnormality.

2.7.1 History of MRI

Nuclear magnetic resonance (NMR) was first demonstrated simultaneously by the groups of Bloch and Purcell in 1946. It is based on the observation that if a sample is placed in a magnetic field and irradiated with a radiofrequency as a specific frequency, a signal is detected and the signal is related to the angular momentum of protons and neutrons in the nucleus known as ‘spin’.

2.7.2 Physics of nuclear magnetic resonance imaging (NMR)

The details of the physics underlying magnetic resonance imaging are complex and can be found in physics or imaging textbooks and a brief summary only is given here.

Magnetic resonance imaging (MRI) exploits the tendency of spinning protons to twist when exposed to a magnetic field and align themselves with it. In living tissue, which is
predominantly made up of water, the protons are almost all hydrogen ions and in MRI they enter a static magnetic field $B_0$, typically of between 1.5 and 9.4T causing them to align themselves with this external field and ‘precess’ (spin in alignment with the field).

Following this an applied radiofrequency (rf) pulse changes the external magnetic field and protons at the same frequency as the ‘rf pulse’ enter a higher energy state. Protons will only change state if the rf pulse is applied at the specific rotational frequency at which the protons are precessing for any given element as described above (this is known as the Larmor frequency).

Although an individual proton’s energy level is determined by the radiofrequency pulse applied, the signal emitted is dependent on the behaviour of a population of protons. In the case of in vivo MRI, the water content (and therefore the hydrogen ion content), varies between particular tissues providing magnetic resonance ‘contrast’ between tissue types.

There is a distribution of protons between two energy states within humans, and the lower-energy state is favoured; thus there are approximately 1 000 004 spin-up protons for every 1 000 000 spin down. Both populations precess around the direction of the external magnetic field ‘$B_0$’ and the net difference in the populations produces a magnetization ‘$M_0$’, which is much smaller than the applied external field.

### 2.7.3 Measuring the signal

Owing to the fact the magnetization produced by the net ‘spin’ of the protons in the body described above is of the order of 1/1000 compared with the externally applied field, it is practically impossible to measure when in line with the field, and so a brief
radio-frequency pulse (RF) is applied, effectively flipping the magnetization field $M_0$ at $90^\circ$ to $B_0$. This brief radio-frequency pulse is applied at the Larmor frequency and a strength $B_1$.

Rotating $M_0$ by the application of $B_1$ results the spins being aligned with one another, perpendicular to $B_0$ and the signal transmitted from these protons is detected by voltage induced in a receiver coil, sensitive to magnetization perpendicular to $B_0$ field. The strength of $B_1$ can be varied producing different ‘flip angles’ of $M_0$. The protons’ spin is only aligned for a short time and then the spins move out of phase with respect to one another leading to a decay in the signal.

2.7.4 Relaxation Times:

Immediately following the application of the RF pulse, the magnetization is maximal, perpendicular to $B_0$ (in the transverse plane), and effectively 0 in the z-direction (parallel with $B_0$). Following this the magnetization in the transverse direction decays and that in the longitudinal direction changes exponentially until a state of equilibrium is reached. The time for this decay to zero to occur in the transverse plane is the $T_2$ (spin-spin) relaxation time. $T_1$ relaxation (spin-lattice) describes the time for the magnetization in the longitudinal direction to return to a state of equilibrium following the end of the RF pulse.

2.7.4.1 $T_1$ relaxation:

$T_1$ times depend on the amount of motion of molecules at the Larmor frequency for a given substance and $T_1$ weighted imaging sequences are designed to be sensitive to the differences in this amount of motion between tissues. In practice, this means that the $T_1$ times for substances such as CSF which have a large quantity of free water and
consequently a high proportion of molecules moving faster than the Lamor frequency (with a long T1 time) will appear darker than those tissues in which molecules move at a lower frequency resulting in a shorter T1 time (e.g. fat). T1-weighted sequences exploit this difference in T1 relaxation time.

2.7.4.2 T2 relaxation

T2 is dependent on the interactions between precessing protons (‘spins’) in the transverse plane. Following the RF pulse, all protons will spin in the same direction at the Lamor frequency, but as time passes, they move towards one another and are subject to one another’s magnetic field resulting in fluctuation of the angular frequency. These fluctuations gradually lead to a loss of transverse magnetization. Time to echo (the time from RF pulse to signal transmitted from to the tissue) and TR (repetition of RF pulse) should be long enough to allow T1 to have completely elapsed in a T2 sequence.

2.7.4.3 T2* sequences

Gradient Echo applied to T2 weighted sequences produce ‘T2* weighted images’. These images are more sensitive to ‘magnetic field susceptibility’ as they depend on variations in the magnetic field. Effectively, the varying magnetic properties of substances scanned (air within the bony sinuses within the head for example), change the local magnetic field which affects the apparent spin-spin relaxation time following the RF pulse, causing very rapid T2* relaxation. This is very prominent at air/tissue interfaces, but the effect is also sensitive to the concentration of deoxyhaemoglobin in tissue surrounding vessels, meaning it is suitable for the detection of Blood oxygen level dependent (BOLD) signal change in fMRI.
2.7.5 Structural MRI in Epilepsy

MRI is well known to be superior to computed tomography (CT) in the detection of the pathology underlying focal epilepsies in both adults and children (Kuzniecky et al., 1993b; Sperling et al., 1986; Theodore et al., 1986a) and identifies abnormalities in around of 75% of patient with focal epilepsy who may benefit from surgery (Duncan 2010). The most commonly identified abnormalities are hippocampal sclerosis, malformations of cortical development (focal cortical dysplasia and others), vascular malformations, tumours, and acquired cortical damage. Some of the more important findings specific to hippocampal sclerosis and FCD are summarised below along with some of the novel approaches to neuroimaging in MRI normal cases.

2.7.5.1 Structural MRI in Temporal lobe epilepsy:

Reliable detection of hippocampal sclerosis, the most common lesion seen in refractory focal epilepsy (accounting for 32% of structural abnormalities in temporal lobe epilepsy), has been established for many years, and can be quantified by manual volumetry or T2 relaxometry (Jackson, Berkovic et al. 1990, COOK, FISH et al. 1992, Van Paesschen, Connelly et al. 1997) and MRI identified hippocampal atrophy has been shown to correlate well with hippocampal loss, particularly in the CA1 sub-region (Van Paesschen, Connelly et al. 1997). Automated methods using voxel based morphometry have been developed to allow faster, reliable detection of the lesion (Bonilha, Halford et al. 2009), while a similar approach using surface mapping has also yielded promising results.

Standard MRI sequences enable unilateral hippocampal atrophy to be assessed visually by an experienced neuroradiologist with asymmetry of up to 20% between sides. Quantitative assessment is a useful technique to detect differences below this
(Bartlett, Symms et al. 2007, Farid, Girard et al. 2012), although it probably only increases sensitivity to around 90-95%.

- **Advanced imaging in TLE: Identification of hippocampal sub-fields**

The development of advanced MRI sequences such as the PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction), which compensates for subject movement, appears to allow more detailed delineation of structures within the hippocampus (Eriksson, Thom et al. 2008). High field MRI has also been shown to be a valuable tool in the delineation of hippocampal sub-fields, correlating well with histo-pathological findings (Mueller, Laxer et al. 2009).

- **Understanding the Epileptic network in TLE: Structural Changes**

Voxel based morphometry has been a successful technique in the investigation of TLE; in particular changes are reported outside of the mesial temporal structures adding support the concept of TLE reflecting abnormalities not only in the mesial temporal structures, but also in structurally and functionally connected regions elsewhere in the brain (Keller and Roberts 2008). In studies of mesial temporal lobe epilepsy, there are reports of changes in the parahippocampal gyri, thalamus and entorhinal cortex, while more widespread changes were observed in neocortical temporal lobe epilepsy (Pell, Briellmann et al. 2004). It should be born in mind, that the technique produces variable results in TLE as there are often susceptibility artefacts in the temporal lobes as mentioned above.

**2.7.5.2 Malformations of cortical development**

Structural MRI allows the visualization of gross abnormalities such as schizencephaly, lissencephaly, band heteroropia and grey matter nodular heterotopia as well as more
subtle regions of focal cortical dysplasia. On MRI, the regions of heterotopia are seen as isointense to normotopic grey matter (Band heterotopia are usually bilateral and approximately symmetrical and typically, the medial border of the lamina is smooth, whereas the lateral border follows the white matter into the crowns of the gyri). The cortex overlying the laminae may appear macrogyric. Polymicrogyria may be visible on high resolution MRI or be indistinguishable from macrogyria / pachygyria (Raymond, Fish et al. 1995).

In Focal Cortical Dysplasia, typical features include blurring of the grey/white matter border, high signal on T2 weighted MRI and a tail of high signal extending from under the region of dysplastic cortex to the underlying ventricle (Duncan 1997). Appearances on MRI may alter over time which may reflect changes in myelination in the maturing brain and there also changes in MRI appearances with seizure induced inflammation. The advent of 3T MRI is particularly relevant in focal cortical dysplasia; up to 20% of patients who have good standard imaging have been shown to have lesions on subsequent 3T MRI, many of whom have malformations of cortical development (Strandberg, Larsson et al. 2008).

Recommended clinical sequences for the optimal detection of FCD have been described and the most recent are listed in the table below:
<table>
<thead>
<tr>
<th></th>
<th>Sequence Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmanpera and Duncan, 2005</td>
<td>T1,T2 weighted proton density and FLAIR images, minimum slice thickness, two orthogonal planes.</td>
</tr>
<tr>
<td>Widess-Walsh, 2006</td>
<td>T1,T2 weighted proton density, FLAIR +/- MR spectroscopy and diffusion tensor imaging</td>
</tr>
<tr>
<td>Woermann, and Vollmar, 2009</td>
<td>Comprehensive protocol (NB, there are different sequences recommended for different ages). Include FLAIR, T2, T2* and T1 weighted volumetric.</td>
</tr>
</tbody>
</table>

**Advanced structural imaging in FCD**

The development of more sensitive and specific imaging techniques for the detection of FCD is of particular relevance as complete resection of the dysplastic cortex is the most reliable independent predictor of seizure freedom following surgical resection (Krsek, Maton et al. 2009), while a significant number of patients with focal cortical dysplasia continue to have normal conventional MRI despite the use of higher field strengths (McGonigal, Bartolomei et al. 2007, Duncan 2010).

Conventional VBM in focal cortical dysplasia has been less promising than in TLE, having poor sensitivity. Other imaging techniques, based on the observation of grey-white matter blurring on conventional MRI, have been more successful, while a new technique, specifically comparing FLAIR sequences calibrated against brain regions in
normal subjects (similar to the technique described as voxel based relaxometry (VBR) was able to identify regions of FCD in 22/25 patients with only one false positive (Focke, Symms et al. 2008).

Diffusion tensor imaging, which allows detailed study of the white matter tracts revealing subtle abnormalities, is also promising in FCD and has revealed abnormalities immediately below the dysplastic cortex (Widjaja, Blaser et al. 2007), while analysis of fractional anisotropy has revealed abnormalities in children with cortical dysplasia extending beyond the region of structural abnormality on MRI, but colocalised with dipoles identified with magnetoencephalography (MEG) (Widjaja, Zarei Mahmoodabadi et al. 2009).

Interest has also grown in the genetics of FCD, and MRI has contributed to these studies; specifically, relatives of patients with focal cortical dysplasia also exhibit grey matter abnormalities even in the absence of focal epilepsy (Merschhemke, Mitchell et al. 2003).

2.7.5.3 MRI abnormalities related to seizures

Epilepsy is a dynamic disease and while structural MRI is essentially a ‘static’ technique, post ictal MRI in small series has shown changes in diffusion weighted imaging compared with interictal studies (Diehl, Najm et al. 2001, Hufnagel, Weber et al. 2003, Oh, Lee et al. 2004) although these are not necessarily specific to the seizure onset zone (Diehl, Symms et al. 2005, Salmenpera, Symms et al. 2006).

During or following status epilepticus, T2 signal change and hippocampal atrophy has been reported in the hippocampi of patients with TLE (Wiesmann, Woermann et al. 1997) (Lansberg, O'Brien et al. 1999, Kim, Chung et al. 2001, Sirven, Zimmerman et al.
2003) as well as children with febrile status epilepticus (Shinnar, Bello et al. 2012). Diffusion weighted imaging is also reported to show increased signal, presumably relating to prolonged hypoxia/hypoperfusion (Milligan, Zamani et al. 2009).

Abnormalities of diffusion have also been seen in both remote cortical and sub-cortical regions (from seizure onset) in status epilepticus (Szabo, Poepel et al. 2005, Katramados, Burdette et al. 2009).

2.7.5.4 Contribution of higher field strength MRI in Focal epilepsy

Recently, scanning at increased field strengths (3T) has been shown to identify or clarify subtle abnormalities, in particular focal cortical dysplasia in 20% of patients who had previously been identified ‘MRI-normal’ (Strandberg, Larsson et al. 2008), although a retrospective analysis of 804 patients scanned at both 1.5 and 3T by the same group suggested the increase in yield of MRI abnormality was only 5% (Winston, Micallef et al. 2013), raising the possibility that the use of appropriate sequences and expert interpretation may contribute to accurate diagnosis more than higher field strength, adding to evidence from another group that different lesions are identified on 3T scans compared with 1.5T, but the yield is not necessarily increased (Zijlmans, de Kort et al. 2009).

In addition to higher field strength there may be some additional value from using techniques such as voxel based morphometry in ‘MRI normal’ subjects, but the clinical utility is yet to be established (Salmenpera, Symms et al. 2007).

2.7.6 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) of hydrogen 1H nuclei in vivo is a well established technique. In MRI it is generally acceptable to consider that the resonant
frequency of any particular nucleus depends only on the applied magnetic field (B0).

In fact the stimulated nuclei are also subject to the local environment. Nearby electrons and other nuclei have small but significant effects on the net field to which the nucleus is exposed. From the Larmor equation this will alter the frequency at which that nucleus will resonate. MRS experiments aim to separate and measure different metabolites on the basis of this variation in resonant frequency or chemical shift. The most frequent compounds studies in vivo are $^1\text{H}$, $^{13}\text{C}$ and $^{31}\text{P}$, but in epilepsy compounds of particular interest are Creatine containing compounds (which reflect local energy metabolism), N-acetyl aspartate (NAA, reflecting specific aspects of neuronal integrity) and myo-inositol which reflects a combination of glutamate and GABA. MRS findings are expressed as ratios between concentrations of these compounds.

2.7.7 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a neuroimaging technique that, by measuring the random motion of water molecules in various structures (known as Brownian motion) using MRI, allows the differentiation of different tissue types (and is especially useful for visualising white matter tracts in the brain). Cellular structures limit the natural diffusion of water molecules meaning there is a difference in the potential diffusion range of water molecules depending on tissue type, referred to as the diffusion coefficient.

MRI can be used to measure the diffusion properties of various tissues, by exploiting the magnetic properties of water molecules. The diffusion tensor is obtained by measuring the diffusion property of each voxel in three directions, and maps of apparent diffusion coefficient (ADC) allows the difference in diffusion between tissues
to be measured (found by subtracting T2 from diffusion weighted image (DWI). This is routinely used in clinical imaging in a variety of settings (Pierpaoli, Jezzard et al. 1996).

Analysis methods can be applied following the DTI acquisition to identify white matter tracts from a user-defined starting point (seed point) based on the identification of the direction of maximal water diffusion using various mathematical methods.

Diffusion tensor imaging has been used extensively in the study of focal epilepsy and an extensive discussion of its application is beyond the scope of this work – I have summarized some of the more important findings below. The most pertinent findings with respect to this thesis are the observations by many groups, that DTI abnormalities in epilepsy extend beyond the epileptogenic zone, giving support to the concept of a plastic epileptic network, such as is seen in EEG-fMRI studies.

2.7.8 Diffusion tensor imaging in Epilepsy

2.7.8.1 DTI in Temporal lobe epilepsy

In temporal lobe epilepsy (TLE), ADC values have been used to lateralise the epileptic focus, but only when unilateral hippocampal sclerosis is seen on conventional structural MRI (Wehner, Lapresto et al. 2007). These abnormalities extend beyond the hippocampus, suggesting structural abnormalities extend into the epileptic network rather than being isolated to the structures in which seizures are generated even when conventional imaging is normal (Gross, Concha et al. 2006, Gong, Concha et al. 2008).

A more recent study, confirmed diffusion abnormalities outside of the hippocampus and also extending into extra-temporal and contralateral region (Focke, Yogarajah et al. 2008) using a voxel based method, while there have also been investigations into
clinical symptoms in TLE suggesting diffusion abnormalities related to interictal psychosis (Flugel, Cercignani et al. 2006).

In addition to the study of the epileptic network in TLE, DTI has been used to study structural pathways related to visual function (as mentioned previously), memory and language, which are important in the planning of surgical resection (Yogarajah, Focke et al. 2009, Yogarajah, Focke et al. 2010, Winston, Daga et al. 2012).

2.7.8.2 Other focal epilepsies

Many studies of focal epilepsy of mixed aetiology have shown here that there abnormalities in diffusion associated with both temporal and extra-temporal epilepsy which affect not only the irritative and epileptogenic zones, but also areas beyond (often those which are more connected) (Thivard, Adam et al. 2006, Guye, Ranjeva et al. 2007). Similar observations are also seen in malformations of cortical development (Eriksson, Rugg-Gunn et al. 2001, Trivedi, Gupta et al. 2006, Widjaja, Zarei Mahmoodabadi et al. 2009), adding weight to the assertion that the structural epileptic network involved in malformations of cortical development extends beyond the abnormality seen on structural MRI.

2.7.8.3 Changes related to seizures

In patients with epilepsy, temporary altered diffusion related to oedema has been noted in status epilepticus (Wieshmann, Woermann et al. 1997, Lansberg, O'Brien et al. 1999) which appears to resolve on follow up studies (Szabo, Poepel et al. 2005). In addition DTI has also shown more permanent abnormalities which eventually leads to atrophy within the affected region (Lansberg, O'Brien et al. 1999, Gong, Shi et al. 2008).
2.8 The role of additional non-invasive techniques in localising focal epilepsy

It can be seen from the discussion above, that despite progress in structural MRI, including the development of advanced techniques, which have improved the detection of abnormal tissue, there remain a group of patients in whom MRI reveals little about the seizure onset zone or the epileptic network. There is therefore a need for other non-invasive techniques, which have developed alongside these advances.

2.8.1 Radionuclide imaging

Both ictal perfusion single photon emission computed tomography (SPECT) and interictal fluorodeoxyglucose positron emission tomography (FDG-PET) can provide information in the presurgical evaluation of intractable partial epilepsy. These functional imaging modalities reflect dynamic seizure-related changes in cerebral cellular functions. The techniques have been shown to provide added value in localising the ictal onset zone in patients with normal MRI - a particularly challenging group for presurgical evaluation. Regions of reduced glucose uptake indicated by interictal FDG PET-hypometabolism are associated with the irritative zone, while clinical studies suggest that a focal increase in blood flow associated with focal seizures can be detected by using a radiolabelled tracer at the onset of a seizure.

The largest study of this phenomenon in pre-surgical evaluation looked at 89 patients with refractory focal epilepsy and normal MRI and found that interictal FDG-PET had a diagnostic sensitivity of 44% while ictal SPECT had a sensitivity of 41% at a lobar level (Knowlton, Elgavish et al. 2008) However, the site of ictal SPECT was not related to the resected area post-operatively (Knowlton, Elgavish et al. 2008) as due to its low temporal resolution, ictal perfusion SPECT hyperperfusion patterns often contain both the ictal onset zone and propagation pathways.
2.8.2 PET

2.8.2.1 Fluorodeoxyglucose

PET (positron emission tomography) is most the most established functional interictal technique used to in focal epilepsy. It was initially developed using radio-labelled fluorodeoxyglucose (FDG-PET), to enable the identification of areas of reduced glucose uptake which reflect areas of abnormal cerebral metabolism and correlate well with regions of relative cerebral dysfunction observed in focal epilepsy.

In temporal lobe epilepsy, the most widely studied group, it has been demonstrated that FDG-PET is a useful lateralising tool with hypometabolism observed in the affected side. It appears that FDG –PET studies, while being a useful lateralising tool show widespread hypometabolism in the affected lobe, rather than a more specific effect restricted to the irritative or epileptogenic zone. Studies have been carried out in patients with both lesional mesial temporal lobe epilepsy (hippocampal sclerosis)(Valk, Laxer et al. 1993) and MRI negative temporal lobe epilepsy (Carne, O’Brien et al. 2004) in whom, unilateral hypometabolism was observed. The authors suggested that the FDG PET abnormality may allow differentiation of MRI negative form positive TLE as a distinct syndrome.

In addition to its lateralizing ability, FDG-PET metabolism has also been shown to be altered in regions remote from the temporal lobe in patients with temporal lobe epilepsy in particular the frontal lobes, suggesting its role may be in understanding more general cerebral dysfunction in epilepsy rather than specific localization of the seizure onset zone. Post-operative data showed that following temporal lobe resection, their were areas of hypometabolism in deafferented areas while seizure propagation pathways showed a relative increase in metabolism which the authors suggested may provide a
useful understanding of functional changes following surgery. In addition further data suggests that the extent of FDG-PET hypometabolism in the temporal lobes may predict post-surgical outcome, although the concept of it is clear that PET does not accurately identify the seizure onset zone as discussed above (Vinton, Carne et al. 2007).

Beyond its use in mesial temporal lobe epilepsy, the role of FDG-PET is less clear-cut. The study of 89 patients with refractory neo-cortical epilepsy referred to above reported that FDG-PET in the temporal lobe cases studied was significantly associated with outcome following surgery and diagnostic sensitivity (localisation of the seizure focus) was more in the TLE group than in extra-temporal cases (Lee, Lee et al. 2005).

Recently there have been specific evaluations of the role of FDG-PET in pre-surgical evaluation for TLE. A meta analysis suggests that lateralised PET was predictive of good post operative outcome, but that it did not add value in patients who already had localising MRI and EEG (Willmann, Wennberg et al. 2007), while a cost-benefit analysis has shown similar findings (O'Brien, Miles et al. 2008).

The findings in frontal lobe epilepsy have been less clear cut, with bilateral abnormalities reported in a significant number of cases. Ictal scans can be useful; however, the long duration for steady-state uptake of glucose (of the order of 20+ minutes compared with partial seizures, which are typically less than a couple of minutes) often leads to scans that contain a difficult-to-interpret mixture of interictal, ictal, and postictal states. Thus, presurgical epilepsy FDG-PET scans are typically performed in the interictal state with the goal of detecting focal areas of decreased metabolism, relative hypometabolism, that are presumed to reflect focal functional disturbances of cerebral activity associated with epileptogenic tissue. What is still
remarkable about FDG-PET is that the cause of hypometabolism in and near epileptogenic regions of brain remains unclear.

2.8.2.2 Other Ligands

Although not in current routine clinical use, the role of PET utilizing alternative ligands to FDG-PET has been investigated.

2.8.2.3 11-C- Methionone:

This has been most useful in the detection of gliomas and one study suggested it might be useful to differentiate epileptogenic slow growing DNETs (dysembryonic neuroendothelial tumours) from gliomas, but it has not been helpful in the pre-surgical evaluation of epilepsy otherwise.

2.8.2.4 Flumazenil-PET

The use of flumazenil as a ligand in PET was motivated by the fact that it specifically binds benzodiazepine receptors and it is known that dysfunction of GABA, and specifically GABA inhibition is important in the generation of seizures. An initial study in temporal lobe epilepsy in patients with hippocampal sclerosis demonstrated hypometabolism concordant with MRI and FDG PET findings in 89% of the patients studied (Ryvlin, Bouvard et al. 1998). Although FMZ-PET areas of hypometabolism were noted to be smaller than FDG-PET hypometabolic regions (Koepp, Hammers et al. 2000), a further level of localization has not been demonstrated.

Two studies in patients with normal MRI and flumazenil PET demonstrated widespread abnormalities in the grey and white matter particularly in periventricular regions leading the authors to the conclusion that this might represent abnormalities in neuronal
migration not observed on MRI; however no further localizing information was obtained for pre-surgical evaluation (Hammers, Koepp et al. 2003).

In summary therefore, interictal PET has and continues to be a useful investigation for understanding the neurobiology of epilepsy and the evolving use of new ligands is promising, but in terms of pre-surgical evaluation at the individual patient level, its utility is restricted to those patients with temporal lobe epilepsy in whom the laterality of the seizure focus is not known.

2.8.3 Ictal SPECT

Ictal SPECT is a complex technique which is very user dependent. Unfortunately it may take up to 30 seconds for the ligand to reach the brain, which limits the utility of the method in determining the seizure onset (Dupont 2008). By the time the images are taken, seconds after the administration of the ligand, it is likely that the seizure will have developed and it has been observed that the changes which occur with ictal SPECT commonly reflect seizure propagation rather than the seizure onset zone. Even where the injection is given very early (<5 seconds) in one study, 73% of the examinations were found to show areas of propagation exhibiting areas of hyperperfusion in addition to the seizure onset zone although concordance between these areas and electroclinical data is significant in cases where the injection is given within 20 seconds of seizure onset (Fukuda, Masuda et al. 2006). In addition to the use of SPECT to localise focal areas of hyperperfusion associated with the seizure onset zone, investigation of the behaviour of remote brain regions has also been possible with studies demonstrating hypoperfusion in the association cortices at the time of seizure onset\textsuperscript{125}. These studies have provided the basis for the use of fMRI and EEG techniques to investigate these effects further in recent years.
Its use has been improved by coregistration with MRI and subtraction from interictal SPECT (SISCOM), but the peak region of hyperperfusion may reflect propagation or even false lateralization (Huberfeld, Habert et al. 2006). SPECT has limited specificity and sensitivity although analysis techniques to improve this are being developed.

In general, radioligand studies have been useful in lateralizing the seizure onset zone and interictal PET has been extremely useful in understanding the underlying mechanisms of the evolution and consequences of seizures. However they offer limited localizing information beyond this and the need for further non-invasive functional imaging techniques for pre-surgical candidates remains.

2.9 EEG and epileptogenesis

Scalp EEG remains the initial routine investigation for the evaluation of both focal and generalised epilepsies, since it was first developed by Berger in the 1920s, and involves the indirect recording of neuronal activity using electrodes applied to the scalp and connected to an amplifier. In order to understand the basis of the EEG signal, I have summarised some of the neurophysiological features underlying epileptic activity. The details of these processes not fully evaluated and a more comprehensive discussion is available in various authoritative reviews (de Curtis and Avanzini 2001, Niedermeyer and Lopes da Silva 2005).

2.9.1 Physiological mechanisms of epileptogenesis

Individual neuronal recordings from epileptic foci often show characteristic episodes of membrane depolarisation accompanied by bursts of action potentials occurring synchronously in groups of neurones. While this behaviour is not unique to epileptic
foci, and can be observed particularly in tissue, which is susceptible to epileptic activity (e.g. hippocampus and amygdala), there is an increase in burst firing in individual neurones in epileptic foci leading to ‘hypersynchrony’ (Isokawa-Akesson, Wilson et al. 1987). It is this hypersynchrony which results in the membrane depolarisation or paroxysmal depolarising shift (PDS) and the extracellular changes causing the interictal spike. Spread of the hypersynchrony to nearby populations of neurones, may result in the generation of seizures. The mechanisms by which intracellular DPS results in the generation of hypersynchrony and changes in the extracellular field potentials in neuronal populations appear to vary according to the structure of the tissue involved.

Interictal epileptiform discharges (IEDs) in both experimental and human focal epilepsies, are expressed by high-amplitude (>50 μV), fast electroencephalographic (EEG) transients, defined as interictal spikes (ISs), habitually followed by a slow wave that lasts several hundreds of milliseconds. The term IS includes rapid potentials traditionally defined as spikes (synchronous events with a duration less than 50 ms) and longer potentials (50–200 ms duration) known as sharp waves (de Curtis and Avanzini 2001). In this thesis the term IEDs is understood to encompass both these event types, seen on scalp EEG as the neuronal substrate of both is likely to be similar. ISs often occur periodically and or may cluster in brief paroxysms (‘bursts’) with similar spatial distribution. Sometimes the events or paroxysms describe a wider distribution, reflecting the involvement of a wider area of cortex and probably also involving underlying sub-cortical structures. Although IEDs may be generated by the same neuronal population as those involved in the generation of epileptic seizures, they are not, as a general rule, a direct precursor to ictal discharges, which are characterized by a completely different EEG pattern mediated by different neuronal mechanisms.
2.9.2 Initiation and propagation of the interictal spike

The exact mechanism of generation of the synchronous firing of neuronal populations leading to epileptic discharges remains the subject of some debate; various experimental models suggest both deficient and excessive GABA-ergic activity reflecting abnormally increased, decreased or preserved inhibition (de Curtis and Avanzini 2001), suggesting that a model of imbalance in inhibitory and excitatory imbalance causing epileptic activity is probably too simplistic. Hypersynchrony may reflect either excitatory activity or recurrent inhibition as suggested in one early study, which showed a prolonged period of inhibition following stimulation to synchronously firing hippocampal neurones.

2.9.3 Role of Excitatory synaptic transmission.

In epileptic tissue, the burst firing of neurones is increased resulting in temporo-spatial summation of post-synaptic potentials, a process which is blocked by inhibition of NMDA mediated (glutamate) transmission and conversely that these bursts are caused by activation of NMDA receptors in neocortical slices from both adults with mesial TLE and children with intractable epilepsy (Avoli, Louvel et al. 2005). This results in the PDS discussed above and initiation of the interictal spike.

One hypothesis for the generation of epileptiform discharges is that a persistent enhancement of excitatory glutamatergic transmission (via AMPA, NMDA and Ca mediated mechanisms) underlies their generation as observed in the hippocampus in animal models (de Curtis, Radici et al. 1999). Recurrent and persistent excitation via these mechanisms results in a particular post-synaptic potential known as an ‘after-discharge’ which is reported in models of chronic epilepsy, suggesting that not only is
enhanced excitatory transmission involved in the generation of the spike, but also that it has a greater role in establishing epileptogenesis.

2.9.4 Role of inhibitory Activity

In vitro experiments with human neocortical slices emphasise the importance of inhibitory (GABA mediated) activity in the generation of interictal events and it has been suggested that this results in a refractory period between spikes during which the discharge threshold for the generation of further epileptic activity is raised; effectively meaning that the spike may have some role in preventing the onset of seizures (de Curtis, Librizzi et al. 2001). Further studies of icEEG in humans in vivo together with calcium imaging have also demonstrated that interictal epileptiform activity is dependent on GABA mediated inhibition rather than simply being an ‘imbalance’ in inhibitory and excitatory activity (Sabolek, Swiercz et al. 2012).

2.9.5 The basis of the EEG signal

As has been discussed above, burst firing of populations of neurones and alterations in the inhibitory and excitatory transmission results in changes in the extracellular membrane potentials across populations of neurones. The extracellular currents generated depend on the synaptic input; in the case of an inhibitory post-synaptic potential, the resulting current is negative, while if an EPSP is generated, the resulting current is positive. There results a current sink in the case of an EPSP as current is directed across the cell gradient into the cell, while a current source is generated in the case of an IPSP at the synapse, while the opposite is true at some distance from the synapse.
At a macroscopic level, therefore, field potentials are generated by groups of activated neurones which behave in simple terms as a dipole layer, perpendicular to the cortical surface (with amassed post-synaptic potentials determining whether the extracellular potential is positive or negative), and with the appropriate spatial organisation can be sources of field potentials which are measured at a distance using electrodes. There is sufficient experimental evidence, reviewed in various authoritative reviews to suggest that post-synaptic potentials are the chief contributor of the recorded EEG signal (Niedermeyer and Lopes da Silva 2005). Given the fact that the dipoles are generated perpendicular to the cortical surface, the EEG signal is mostly generated in the convex surfaces of the gyri and dipoles generated within the walls of sulci will cancel one other out, such that the scalp EEG is essentially blind to these deeper sources (Nunez and Silberstein 2000). It should be noted that a much larger area of cortex is required to generate an 'event' on scalp EEG compared with direct recording at the cortical surface (Tao, Baldwin et al. 2007). The temporal pattern of EEG is also dependent on these populations of signals; it has been shown that electrical fields recorded at the cortex appear to spread in different directions. This spread means that EEG events recorded at the scalp appear longer than when recorded at the cortical surface owing to a lower resolution temporal sampling with greater distance from the source of the field potential. In addition the folded macroscopic structure of the cortex together with the complex multi-laminar neuronal system meand the relationship between neuronal sources and the recorded EEG is complex (Megevand, Quairiaux et al. 2008). There are increasing efforts to model the signal using more complex spatial representations and temporal models of neuronal populations (Ray, Tao et al. 2007).
2.9.6 Recording EEG

Scalp EEG was first recorded in humans by Berger in 1929, using two electrodes. The technique developed and in 1958, a consensus opinion was published on electrode placement resulting in the now commonplace ‘International 10-20 system (see Figure 2-1: Typical layout of scalp EEG electrodes (Niedermeyer and Lopes da Silva 2005)). The scalp, skull and meninges act as a low pass filter in scalp EEG and have poor conductivity resulting in increased impedance which is minimised by the use of gels containing conducting electrolytes between the electrode and the scalp. An impedance of below 5kΩ is generally accepted as adequate following skin preparation (ACNS 2006).

![Figure 2-1: Typical layout of scalp EEG electrodes](image)

Figure 2-1: Typical layout of scalp EEG electrodes
2.9.6.1 Filters

Low and high pass filters can be varied according to which signals are sampled. A notch filter at 50Hz is typically used to remove mains electrical artefact.

2.9.7 Normal EEG

The normal EEG varies throughout life and maturational changes will not be discussed here in detail. There is variation in EEG signal depending on state (awake rest, task and sleep), which are described extensively in authoritative texts (Panayiotopoulos 2004, Niedermeyer and Lopes da Silva 2005). The salient features will be briefly reviewed here, some of which investigated with EEG-fMRI.

2.9.7.1 Alpha frequency activity

In normal conscious rest, the most striking feature of the EEG is posterior dominant rhythm, initially described by Hans Berger in 1929, which may have a right predominance and is in the range 8-12 Hz (alpha rhythm). It is attenuated by eye opening, stimulus etc, and appears to have different characteristics depending on whether it is generated in cortical or sub-cortical regions (primarily the thalamus) and it has been suggested that cortical alpha derives from cortico-thalamic interactions (Lopes da Silva, Vos et al. 1980). Alpha power in these regions has also been shown to be reduced by brain activation or cortical excitability.

2.9.7.2 Beta and gamma frequency activity

Higher frequency activity on the scalp EEG has been the subject of much interest and is related to various physiological factors. Beta frequency (15-30Hz) activity is
generally considered to be associated with mentation or arousal initiated by brainstem activity, which suppresses the lower frequency rhythms of rest.

2.9.7.3 Low frequency activity - theta and delta oscillations

In sleep, the posterior dominant rhythm attenuates to be replaced by lower frequency components, initially in relative isolation and then increasingly dominating the record.

In light sleep, typical features such as vertex sharp wave and brief runs of fast activity called ‘sleep spindles’ appear, sometimes in combination (‘K-complexes’). As subjects progress to deeper stage 3 and 4 sleep, the EEG record is dominated by generalised slow activity in the theta (4-7 Hz) and Delta (1-3Hz) ranges.

2.9.7.4 Task related activity

The EEG is more variable during concentrated activity and may exhibit more artifact in addition to physiological features, as subjects often move much more during purposeful activity. Features such as central mu rhythms may be observed. On intracranial recordings, where there is no impedance from the skull, tasks are typically associated with fast gamma (>20Hz) activity, which at the highest frequencies is difficult to see on scalp EEG.

2.9.8 The Routine (interictal) EEG in Epilepsy

The use of EEG in the diagnosis, classification and management of epilepsy continues to be based on the clinical interpretation of mono and bipolar recordings using the principles discussed above and has been again been extensively reviewed in detail in a number of authoritative texts (Binnie and Stefan 1999) (Panayiotopoulos 2004, Niedermeyer and Lopes da Silva 2005). A brief summary of some of those features,
most relevant to this work will be discussed here. It should be born in mind that epilepsy remains a clinical diagnosis and the EEG is only diagnostic if seizures are seen during the recording with concomitant ictal EEG changes.

The EEG is has a specificity of 78-98% in epilepsy based on the findings of interictal epileptiform discharges (IEDs), but is far less sensitive (25-56%) (Smith 2005). In practical terms, therefore, it is not a diagnostic tool per se and the interpretation of the scalp EEG is dependent on the clinical situation of the patient. The yield of EEG can be improved by various manoeuvres; the inclusion of sleep increases sensitivity to 80-85% while increased length of recording improves yield further (Binnie and Stefan 1999). ‘Epileptiform abnormalities’ (spikes and sharp waves) are often seen in the context of underlying cerebral dysfunction of other causes (e.g. Alzheimer’s disease, encephalitis, Prion disease) in the absence of epilepsy (Smith 2005) and can also occur in a minority of the normal population.

### 2.9.8.1 Interictal EEG in Temporal lobe epilepsy

Scalp EEG is increasingly recognised as useful in the lateralisation of temporal lobe epilepsy, with investigators reporting that where the majority of IEDs are recorded over one temporal lobe, most or all seizures were ipsilateral in 90-95% of cases (Alarcón, Kissani et al. 2001). Interestingly the majority of patients with bilateral temporal IEDs on scalp EEG also have a unilateral seizure focus (So, Gloor et al. 1989). When patients also have ipsilateral hippocampal atrophy, the sensitivity of EEG rises in temporal lobe epilepsy, but with bilateral hippocampal abnormalities on MRI, it can be falsely lateralising.
2.9.8.2 Interictal EEG in Extra-temporal epilepsy

In extra-temporal lobe epilepsy, there is less data, partly as the groups of patients are much more heterogeneous. One study assessed 126 patients with extra-temporal partial seizures and found only 21% IEDs arising from a single focus. Follow up after resection, found that the most significant predictor of good surgical outcome in this group was unilateral EEG spike focus (Holmes, Kutsy et al. 2000). In occipital lobe epilepsy, studies have chiefly been in children, often those with the so called ‘benign epileptic syndromes’ (Gastaut type occipital lobe epilepsy and Panayiotopoulos syndrome) which are characterised by specific EEG features. By definition seizures in these children tend to resolve with maturation and they do not undergo resection, so the relationship between EEG abnormality and resection is not relevant in this group. In occipital lobe epilepsy with an underlying structural cause, the interictal EEG is often not helpful for localisation (posterior, often posterior temporal abnormalities are often detected in OLE) (Taylor, Scheffer et al. 2003), presumably relating, in part, to the fact that much of the occipital cortex lines the walls of the interhemispheric fissure, and EEG is not sensitive to these regions.

2.9.8.3 The routine EEG in generalised epilepsy syndromes

The pathophysiology of the spike and wave discharge was first described in the 1940s, where it was shown in cats, that 3Hz electrical stimulation of the midline thalamic nuclei resulted in spike and wave discharges in the cortex. Williams went on to demonstrate that 3Hz spike and wave discharges in humans arose from the thalamus. That abnormal oscillations in the thalamo-cortical circuitry give rise to spike and wave discharges is now established (Avoli and Gloor 1982), but the generators of this abnormal activity remains the subject of debate with some authors favouring a cortical
generator, others favouring sub-cortical structures and some groups pointing to both (Blumenfeld 2005). fMRI experiments have contributed further evidence to this debate and are discussed in section 2.13.4.7)

2.9.9 Ictal Scalp EEG in Epilepsy

The neurophysiological changes which take place at seizure onset continue to be the subject of intense investigation and debate, and therefore explanations for the changes observed on EEG continue to be evaluated.

Experimental evidence and intracranial recordings in humans both note the onset of low-voltage ictal fast activity within the seizure focus, coupled with a reduction in background slow activity (Alarcon, Binnie et al. 1995, Alarcón, Kissani et al. 2001, Wendling, Bartolomei et al. 2003). The reflection of this on scalp EEG is an attenuation or ‘ictal flattening’ in the background in a very localised region activity (Binnie and Stefan 1999, Blume 2001). Other EEG patterns at seizure onset include rapid repetitive focal spikes, or more widespread rhythmic activity, the latter often seen when scalp EEG has been insensitive to seizure onset. In focal seizures, electrographic onset is often followed by clinical onset (marred by motion artefact on the EEG) and a period of post-ictal slowing may follow (Binnie and Stefan 1999)

In complex partial (‘dyscognitive’ in the 2010 classification) seizures, the ictal flattening described above may be followed by a build up of rhythmic activity, starting typically in one region and evolving in distribution and frequency to involve other areas, sometimes becoming generalised (Blume 2001). In the immediate post-ictal period there may be background focal or global slowing as the seizure terminates. Focal seizures are not always associated with changes on scalp EEG.
2.9.9.1 Localising value of ictal EEG

Several studies have assessed the value of ictal scalp EEG in localising seizure onset, using intracranial EEG or post-operative outcome as validation. In the largest of these studies, which analysed 486 ictal recordings in 72 patients with focal epilepsy, it was found that 72% of patients had at least one localising ictal EEG, with the ictal onset most commonly localised in temporal lobe epilepsy. The same study found that false localising information was most common in occipital and parietal epilepsy (Foldvary, Klem et al. 2001).

The most common abnormality in ictal scalp EEG in mesial temporal lobe epilepsy is rhythmic activity in the theta (5-7Hz) range usually over the side of seizure onset. While ictal EEG continues to be of localising value, in reality the clinical evaluation is a combined with other techniques in particular MRI. The combination of unilateral temporal spikes on EEG with unilateral hippocampal sclerosis/atrophy on MRI was concordant with seizure onset in 97% of cases in one study, which suggested that it might, in fact not be necessary to record ictal seizure onset when all interictal and imaging data is concordant (Cendes, Li et al. 2000), but a paucity of spikes or lack of unilateral abnormality on MRI, will continue to necessitate ictal recording in many patients.

Ictal changes in frontal lobe epilepsy are particularly difficult to localise with scalp EEG for several reasons; the area is particularly difficult to cover adequately with scalp electrodes, very large and there is often rapid propagation of ictal discharges meaning abnormalities are often widespread and so may add minimal localising or lateralising information (Smith 2005).
2.9.9.2 Ictal EEG in idiopathic generalised (genetic in the current classification) epilepsy

The ictal EEG in generalised seizures is more homogeneous than that observed in focal seizures and usually consists of the abrupt onset of spike and wave discharges. The exact morphology of discharges varies with seizure syndrome and some examples are described below.

Table 2.7 Ictal EEG findings in various generalised epilepsy syndromes

<table>
<thead>
<tr>
<th>Seizure syndrome</th>
<th>Typical EEG change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy</td>
<td>3Hz spike and wave discharges</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Spike/polyspike and wave discharges with variable asymmetry</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>&gt;3Hz spike or polyspike/wave discharges</td>
</tr>
</tbody>
</table>

Atypical findings on ictal scalp EEG are suggestive of symptomatic (structural-metabolic) generalised epilepsies, e.g. Landau-Kleffner syndrome, typically associated with slow spike and wave (<2.5Hz) predominantly involving the temporal regions or Lennox-Gastaut syndrome, in which ‘atypical absences’ and ‘tonic seizures’ occur with slow spike and wave and ictal fast activity. Another indicator which differentiates symptomatic from primary generalised (now referred to as genetic) epilepsy is the presence of an abnormal background.

Other epilepsy syndromes have specific EEG findings, e.g. Hypsarrhythmia with ictal electrodecrement in West Syndrome.
2.9.9.3 Limitations of scalp EEG in epilepsy

Traditionally, the approach to clinical EEG involves interpretation of patterns on a bipolar or monopolar (referenced to one or an average of many electrodes), recording, but scalp EEG has limited spatial resolution and is insensitive to deep sources in particular (Nunez and Cutillo 1995) meaning its use in pre-surgical evaluation for the detection of seizure onset at deep sources is more limited.

The development of high density EEG and digital recordings have improved sensitivity and allowed the study of voltage maps over the scalp and investigation of the underlying electrical sources, (and attempts to solve the ‘inverse problem’ described below). DC EEG also allows the recording of very high and low frequency band EEG, which is potentially very interesting.

2.9.9.4 The Inverse problem and electrical source imaging

Although the recorded EEG signal relates to the activity in underlying populations of neurones, EEG is measured as the potential difference between two points with no ideal reference and different intracerebral sources may produce the same pattern. Thus there are an infinite number of possible configurations of the electromagnetic source for the signal recorded at the scalp, ‘the inverse problem’. Assuming each cortical column is modelled as a separate dipole, adequate sampling of the whole population would require thousands of electrodes. The fact that the number of electrodes is restricted presents a further difficulty in accurately localising the signal. In order to estimate the source of a given EEG signal, the intracerebral source is therefore modelled in various ways, considering the onset and propagation of IEDs (Scherg, Bast et al. 1999). The details of this are beyond the scope of this work, but the most commonly used method uses one or more ‘equivalent current dipoles’
Another approach is to examine multiple sites and find the spatial source which best explains the data (distributed source modelling). The drawback with this approach is that thousands of solutions need to be examined even with relatively few electrodes and a good electro-clinical hypothesis is required to limit the solutions appropriately.

2.10 Magnetoencephalography and Magnetic source imaging (MSI)

Magnetoencephalography (MEG) is similar to EEG, in that it detects field potentials related to neuronal activity, but the sensors are orientated to detect the magnetic field perpendicular to that detected with EEG. It requires a highly specialised scanning system and sessions are limited by the time the subject spends in the scanner in contrast to EEG which can be recorded over very long periods.

2.10.1 Comparison with EEG

MEG is more sensitive than EEG to superficial neuronal sources orientated perpendicular to the scalp (e.g. those within interhemispheric fissures or intergyral sulci) (Agirre-Arrizubieta, Huiskamp et al. 2009, Goldenholz, Ahlfors et al. 2009). A combined MEG and icEEG study showed that it is not sensitive to mesial temporal IEDs however (Agirre-Arrizubieta, Huiskamp et al. 2009). Another advantage over EEG, is that there is virtually zero impedance as the skull and meninges have no effect on the conduction of magnetic field. Perceived advantages of MEG with regard to localization over EEG should be interpreted with caution as conventional and even high resolution EEG, does not often use as many sensors as MEG and therefore the comparison is not necessarily like for like. It should be born in mind that the two
techniques essentially measure the same parameter (albeit with variations in sensitivity) and the problem of multiple possible solutions is common to both.

2.10.2 Validation of MEG/ magnetic source imaging (MSI)

Clinical validation of MEG suggests that it may give localizing information in patients who are undergoing icEEG, which may alter the implantation strategy (Knowlton, Elgavish et al. 2008, Stefan, Rampp et al. 2010). Initial suggestions that MSI might be able to replace icEEG in a study of 49 patients with focal epilepsy (Knowlton, Elgavish et al. 2006) have not been born out by subsequent studies. A large evaluation of MEG, SPECT and PET comparing results with post-operative outcome reported a highly localized MEG to have the highest positive predictive value (78%) of the three techniques (Knowlton, Elgavish et al. 2008).
2.11 Intracranial EEG recording

Given the limitations of scalp EEG discussed above, there is a need for more accurate methods of electroclinical localisation and the gold standard for this is currently intracranial EEG. Despite the evolution of new imaging techniques (advanced MRI sequences, PET, ictal SPECT, electric source imaging, MEG) allowing, improved localisation of the seizure onset zone in some cases, approximately 25% of patients with focal epilepsy will not have the epileptogenic or irritative zone identified using non-invasive techniques. In this group intracranial EEG, a technique initially developed in the 1950s may be used to localise the seizure onset zone. There are other reasons for using invasive EEG:

- Insufficient concordance of non-invasive data on the location of the epileptogenic zone (eg. A lesion on MRI which is remote from the area of ictal EEG providing the possibility of multiple zones being involved in the epileptogenic network),

- When a presumed epileptogenic zone lies very close or is suspected to be involved in eloquent cortex. This allows functional mapping to be performed at the same time as invasive recording

2.11.1 Advantages of icEEG

The limitations of scalp EEG are in part overcome by specific features of icEEG, in particular:

- There is significant impedance from the scalp and skull, meaning that the area of cortex discharging synchronously for interictal activity to be detected by scalp EEG may be up to 10cm²)(Tao, Baldwin et al. 2007). In contrast sub-dural electrodes allow
a more localised region of cerebral cortex to be sampled (<1cm², resulting in greater accuracy in the localisation of EEG).

- The skull acts as a low pass filter meaning high frequency activity observed with icEEG at seizure onset is significantly attenuated or even not observed on the scalp EEG (Wendling, Bartolomei et al. 2003). icEEG electrodes are potentially much closer to the neuronal source which they record resulting in much more accurate recording of seizure onset.

- The scalp EEG has limited coverage of deep sources; 70% of the cerebral cortex lies within deep sulci, meaning that neuronal sources in these regions will not lie tangential to the scalp and so detection of neuronal events is reduced.

### 2.11.2 Methods of recording icEEG

Recording may be carried out acutely at the time of resection (electrocorticography or ECOG) or using temporarily implanted electrodes allowing recording over a prolonged period (usually 1-2 weeks) during which interictal activity, spontaneous seizures and intracranial stimulation can be observed, in addition to seizures following withdrawal of AEDs (anti-epileptic drugs) and sleep deprivation (Spencer 1998). However it should be noted that withdrawal of certain AEDs particularly reductions to very low levels may provide false localising information precipitating seizures which are non-habitual, and may not originate in the epileptogenic zone.

Recordings may be made using depth electrodes or sub-dural electrodes which may be formed as strips or grid configurations allowing recording from a broad area of cortical surface. Combinations of both are used in some patients.
2.11.2.1 Stereotactic EEG (sEEG)

Depth electrodes are usually inserted under stereotactic guidance using navigational systems or a Lexell frame. Multi-contact electrodes are typically used carrying between 4 and 12 contacts (4-8 contacts were used in most of our cohort). They are usually constructed from MRI compatible substances (Spencer SS et al. 1997), allowing post-insertion visualisation of the electrodes on MRI.

This approach was pioneered by Bancaud and Talairach and has subsequently been continued predominantly in centres in Europe. The extensive implantation technique adopted by this school exploits anatomical knowledge of neural networks and aims to delineate so called ‘epileptic networks’ specific to the patient under investigation by correlation of the recording with careful observation of seizure semiology. Electrodes are implanted for a variable period of time to allow the recording of spontaneous seizures and also to carry out stimulations, both to delineate eloquent cortex where resection is close to this, but also to record seizures following stimulation.

Following removal of the electrodes, the identification of the Irritative zone and Epileptogenic zone is made and resection is planned. At the time of resection, awake Electrocorticography (ECoG) may be employed to accurately delineate functional cortex, where there is a risk of compromise.

The nature of this classical stereoencephalography has provided extensive data for the study of normal connectivity and has also allowed extensive study of the behaviour of cortical and sub-cortical structures in focal epilepsy, and in particular enables the detailed evaluation of so-called ‘epileptic networks’ in which structures involved in both the onset and propagation of seizures are investigated. An additional advantage of the
approach is that a greater number of structures can be evaluated, without the use of a large craniotomy as used for sub-dural grids.

A significant drawback of sEEG, is that where a cortical focus is identified, it is more difficult to delineate the boundary- in particular the relationship to eloquent cortex. This is addressed by the use of EcOG acutely at the time of resection, sometimes in combination with an awake craniotomy.

Outcome data on a large cohort of patients studied using this technique suggests the approach is highly successful enabling patients in whom structural imaging is apparently normal to undergo surgical resection with seizure freedom in the structurally normal group quoted to be equal to that of the group in whom there was an evident lesion on MRI in one series(McGonigal, Bartolomei et al. 2007). This is in contrast to earlier studies suggesting that in general patients in whom structural imaging is normal are less likely to be seizure free following resection than those in whom a lesion is evident on MRI. A recent study from the same group also noted that as sEEG samples from spatially distinct structures in the brain, it is possible to delineate regions of ‘epileptic tissue’ which may be structurally normal. The authors found that in focal cortical dysplasia, the presence of discrete a poor outcome compared with patients who had a single epileptic focus(Aubert, Wendling et al. 2009).

2.11.2.2 Sub-dural grid electrodes

Sub-dural electrodes (as the name implies) are arrays of conductive metal disc electrodes in either strip (single row) or grid (several interlinked rows) arrays constructed in flexible plastic layers which are placed on the surface of the brain following a craniotomy and stripping of the dura.
They are typically constructed from a variety of materials including platinum, stainless steel or silver and standard recording electrode are usually between 4 and 8mm in diameter (Nair, Burgess et al. 2008). More recently ‘microelectrodes’ have been used in combination with these electrodes enabling recording from a much smaller population of neurones and very high frequency oscillations (endogenous activity at 250-500Hz).

Electrode arrays can be inserted over the convexity of the cerebral cortex or in the inter-hemispheric fissure for example if seizures are expected to have a medial onset.

Following insertion, the electrodes remain in place while the dura and skull are replaced and then connected to an external amplifier via wires threaded through the surgical incision allowing prolonged recording of intracranial EEG.

This approach is technically similar to electrocorticography (ECoG) in that it involves spatial resolution over the cortical surface and is particularly useful for delineating the borders of lesion (eg focal cortical dysplasia), or when the limit of resection should take eloquent cortex into account (ie where the epileptogenic zone borders or overlaps with primary motor area in the case of frontal lobe epilepsy). The disadvantages of this approach are as follows:

a. It is more challenging to record deep sources and those lying within the sulci as the electrodes only sample from a limited cortical area.

b. As the electrodes lie on the surface of the brain it does not remove the problem of electrical source reconstruction (the ‘inverse problem’ present in the scalp EEG recording).
c. The procedure is more invasive with a large craniotomy required, particularly if extensive spatial coverage is required.

In practice, the choice between using depth electrodes or sub-dural grids and strips is dependent on the pathology and semiology of the patient’s epilepsy and is not necessarily limited to a single type of study in any individual patient. For example in neocortical epilepsy where a discrete lesion is apparent on MRI, a sub-dural grid overlying the abnormality combined with a depth electrode lying within the dysplastic tissue may be optimal to ensure adequate resection and limit potential risk to function.

Both approaches allow the recording of spontaneous seizures, but in addition stimulation studies are used, both to map eloquent cortex and also to provoke seizures which may be similar or dissimilar to a patient’s habitual seizures.

Successful surgical resection following exploration with intracranial electrodes, relies on accurate localisation of a single seizure focus and delineation of the relationship between epileptogenic tissue and the functional cortex, the resection of which would result in deficit, so called functional deficit zone (Rosenow and Luders 2001).

### 2.11.3 Limitations of Intracranial EEG

The use of intracranial electrodes eliminates impedance from the scalp and skull, recording directly from the cortical surface or within the brain tissue. In the case of sEEG, there is a temptation to consider this a recording taken direct from the sources; ie a direct samping of neuronal activity is possible. Several important limitations, however, apply, the most important of which are outlined below.

a. The sampling from a depth electrode is of the order of 1cm$^3$ (Tao, Baldwin et al. 2007) meaning that if the whole cortex were to be
sampled, up to 35000 electrodes would be required. This is clearly impractical, and in reality only 70-100 electrodes are used even in the most extensive recordings. The tissue from which to record therefore requires careful selection and a huge extent of tissue, both normal, and involved in the epileptic network of a given patient is not sampled.

b. The inverse solution is not abolished by the use of intracranial electrodes. Despite the improvement in impedance by direct sampling over the cortex, in the case of sub-dural recording in particular, sampling is over the cortical surface and therefore recording from deep sources is still subject to the inverse problem. In the case of depth electrodes, the link between neuronal activity and the signal recorded on the EEG is still not fully evaluated, although there are ongoing studies using simultaneous scalp and intracranial EEG recordings which are investigating this issue\textsuperscript{65}.

c. Unless MRI-compatible materials are used, the use of intracranial EEG may restrict imaging. Regardless of the materials used, individual MRI sequences must have been tested rigorously with each type of device used to ensure patient safety. Over the course of this work our group has been able to demonstrate the successful use of simultaneous intracranial EEG with MRI including fMRI sequences in vivo (Vulliemoz, Carmichael et al. 2011) and this has now been performed by other groups (Cunningham, Goodyear et al. 2012).

d. Interpretation of seizures is not straightforward. Patients routinely undergo drug reduction to reduce seizures in most centres and so
even spontaneous seizures are not recorded in the patient’s usual state. In addition careful study of the semiology is required as stimulation of structures may produce seizures which are atypical for the patient in question and do not allow identification of a surgical target.

2.11.4 Complications

The most common minor complications with intracranial electrode implantations are nausea and headache.

In addition to this, intracranial infection is the most common major complication with rates reported between 1 and 12% while significant haemorrhage which may be extradural or sub-dural is reported in between 0 and 6% of cases (Hamer, Morris et al. 2002, Burneo, Steven et al. 2006, Fountas and Smith 2007). Aseptic meningitis and CSF leak are other major complications. Permanent disability or death is reported in between 0 and 1% of cases in major series (Burneo, Steven et al. 2006). In addition to these complications, the procedures are expensive, interpretation requires a great degree of skill and the offer of resection following surgery is by no means guaranteed, all of which are motivating factors in the development of non-invasive investigations which aimed at replacing or at least improving the selection of patients undergoing icEEG (Blount, Cormier et al. 2008).

2.11.5 Comparison with Non-invasive Methods of Localisation

Data is emerging on novel localisation techniques which are systematically compared with invasive EEG and outcome following resective surgery. Most of these techniques
are ‘whole brain approaches’ and there is therefore a sampling mismatch between invasive EEG, the gold standard, and the newer techniques.

Systematic comparison has now been made with Magnetoencephalography (MEG) (Knowlton, Elgavish et al. 2008), PET and SPECT and suggests that MEG and high resolution EEG may be valuable tools in delineating the seizure onset zone. These findings have been discussed above.

Prior to this project, comparison of EEG fMRI with intracranial EEG has been limited to case reports and two small series, the first of which suggested that where an activation was observed in close proximity to an electrode, the contact was active (Benar, Grova et al. 2006). A later study specifically addressing the role of EEG fMRI in pre-surgical evaluation noted that EEG fMRI might contribute to the identification of a target for intracranial investigation, but this highly selective approach only assessed patients who had previously been rejected for epilepsy surgery (Zijlmans, Huiskamp et al. 2007). Both studies looked at fewer than 8 cases in whom icEEG and EEG fMRI were carried out. There has therefore been a need for a systematic, prospective comparison of EEG fMRI and icEEG, which is the main theme of this thesis.

2.11.6 Clinical Interpretation of icEEG

Interpretation of these implanted electrode recordings involves evaluation of interictal spikes (typically high amplitude events of the order of ~ 100-500uV) in addition to other abnormalities (eg interictal slowing within the lesional zone). There are various approaches to the interpretation of intracranial EEG recordings, but we have chosen to use the internationally recognised system described by Rosenow and Luders (Rosenow and Luders 2001), described above.
The recording of seizures, both spontaneous and following stimulation, allows identification of a target for resection and the tissue which if resected is most likely to produce seizure freedom (the epileptogenic zone).

It should be born in mind that nomenclature differs between groups; ie Bancaud and Talairach defined the epileptogenic zone as that tissue in which the seizure originates and described a primary irritative zone (the region of cortex giving rise to IEDs and overlapping with the EZ) and secondary irritative zone (region of cortex which gives rise to spikes, but does not overlap with the cortex giving rise to seizures) (Kahane, Landre et al. 2006). The argument for an alternative view of the epileptogenic zone, is that the Luders definition is not meaningful in the case of extensive resection; for example a hemispherectomy as the patient may be seizure free, but one cannot define the seizure onset zone as an entire hemisphere. The definitions of epileptogenic, primary and secondary irritative zones may have implications for our understanding of the behaviour of the epileptic network.

2.11.6.1 Towards understanding of the epileptic network with icEEG

Epilepsy has long been recognized to impact regions of the brain outside of its region of onset (take for example, the impact on cognitive function in patients with long term epilepsy) and has been described as a ‘disorder of functionally and anatomically connected, bilaterally represented sets of cortical and sub-cortical brain structures and regions’ (Spencer 2002). It has become increasingly apparent that even within the epileptic network seizure dynamics are complex and the concept of discrete zones is an over-simplification, albeit useful for the planning of surgical intervention.

Intracerebral EEG has been used to examine the relationship between different regions involved in the generation of seizures, predominantly by groups who use the sEEG
technique described above incorporating novel computational analysis to iEEG data, which is extremely rich in features and can be overwhelming to interpret. This has allowed fascinating insight into the behaviour of the ‘epileptic network’ including elegant experiments which show that there is an evolution in oscillatory activity recorded with sEEG, reflecting neuronal synchrony from highly localized high frequency to more widely distributed lower frequency activity as more regions are recruited into the network (Wendling, Bartolomei et al. 2003). The same group have also used sophisticated modeling techniques to study functional connectivity between regions within the epileptic network, both in simulated and patient data, and specifically how this changes between the interictal state and as a seizure evolves, demonstrating that the influence one region has over another as a seizure evolves fluctuates (Wendling, Bartolomei et al. 2001). By identifying sets of coactivated structures (SCAS), Bourien and colleagues showed that it was possible to extract pairs of functionally connected nodes in a network from interictal data, an approach we have used in our analysis of effective connectivity in fMRI data (Bourien, Bartolomei et al. 2005).

In addition to high frequency activity recorded at seizure onset, there is increasing interest in interictal high frequency oscillations, initially detected with microelectrodes which, in patients with focal epilepsy, appear to be a hallmark of the seizure onset zone (Guggisberg, Kirsch et al. 2008, Jacobs, Levan et al. 2009). Recent evidence, showing that resection of regions giving rise to these ‘HFOs’ results in seizure freedom, suggests that these oscillations are likely to relate to the epileptogenic zone (Jacobs, Zijlmans et al. 2010) as well as occurring in the context of normal physiological function (Guggisberg, Dalal et al. 2007). It seems possible that further study of this high frequency activity, which is common to both interictal and ictal activity, may further understanding of how seizures are generated.
It can be seen from this section, that inter-ictal and ictal scalp EEG are invaluable in the pre-surgical evaluation of epilepsy, but intracranial recording is needed in a minority of cases to allow accurate identification and investigation of the epileptic network. However, the procedure is not without risk, and in a significant number of patients, surgical resection is precluded following implantation. There remains a pressing need to validate novel non-invasive techniques which are able to localise seizure onset more accurately, negating or at least improving patient selection for intracranial EEG.

2.12 Functional MRI: Basic concepts and application in Epilepsy

Function MRI (fMRI) is used to infer neuronal activity based on the historic observation in the 1800s that neural activity results in increased blood flow (reviewed in (Raichle 2000)). Its use in epilepsy encompasses both research and clinical applications and it is particularly attractive allows non-invasive assessment of brain networks involved in both cognitive processing and pathological activity (and therefore, using more sophisticated analysis, the interaction between the two).

2.12.1 The Nature of BOLD contrast

In 1990, Ogawa demonstrated that the intensity of signal in gradient echo (GE) images decreased with increase in oxygen consumption (and therefore an increase in deoxyhaemoglobin (dHb) concentration) around blood vessels (Ogawa, Lee et al. 1990) (Ogawa and Lee 1990). This occurs because dHb is a paramagnetic substance and therefore produces susceptibility gradients or local variation in the magnetic field resulting in a change in the transverse (T2*) relaxation time, (T2* describes the transverse relaxation in physiological tissue and is shorter than conventional T2 owing
to these local inhomogeneties). These local variations or inhomogeneities are related, therefore to blood flow which in the brain varies with the amount of neural activity; therefore the variation in $T_2^*$ or gradient echo signal (or blood oxygen level dependent or BOLD signal) is an indirect measure of neural activity (hence functional MRI).

### 2.12.2 Properties of the BOLD signal

BOLD signal depends on the peculiar properties of the MRI scanner. At 1.5 T, for example, the BOLD signal is more sensitive to blood vessel than at higher fields, meaning higher field strength should result in greater specificity of the BOLD signal for neural activity (Yacoub, Shmuel et al. 2001). The fact that BOLD sensitive to blood vessels can mean that increases in BOLD signal can be seen associated with neural activity (for example visual or auditory stimuli) remote from the region of interest. In addition to the effect of field strength, the method by which the BOLD signal is acquired also results in variability in its susceptibility to blood vessels; for example, BOLD acquired using spin echo is more susceptible to small capillaries whereas that acquired with gradient echo is more sensitive to large draining veins. This suggests that the spin echo sequences are likely to have higher specificity in comparison with gradient echo imaging (Weisskoff, Zuo et al. 1994), although this effect is less marked at higher resolutions (>1mm). The exact contribution of blood flow in vessels of different size (arterioles, venules and large vessels) remains the subject of investigation.

### 2.12.3 Spatial Resolution of BOLD signal

As MRI scanners have improved and field strength has increased, the spatial resolution of BOLD signal change has increased. Structural imaging can achieve resolutions of up to 200-300 µm, but fMRI is limited by the fact that it must be acquired
very quickly (echo planar imaging TRs are typically 1.5-4.5 seconds for whole brain acquisition) and there is relatively low signal to noise ratio resulting in resolutions of the order of 3x3x3mm$^3$ in humans at present which is comparable to that achieved in the data presented in this work (Massimo 2009).

2.12.4 Temporal Resolution

BOLD signal change can only be considered a indirect measure of neural activity and its temporal resolution is limited by the time it takes to acquire a whole brain volume (TR) as well as the haemodynamic response to neural activity; essentially there is a trade off between whole brain coverage and spatial resolution versus temporal resolution. The haemodynamic response to a given neuronal signal peaks at 3-5 seconds.

2.12.5 Neural basis of the BOLD response

BOLD Signal has been shown to best represent responses to local field potentials (LFPs) which relate to integrated neuronal processes involving hundreds of neurones rather than the multi-unit activity (MUA) or spikes represented by the summation of extracellular field potentials from small populations of Pyramidal cells at an electrode tip (NB ‘spike’ here refers to the extracellular field potential generated by neural activity not the interictal epileptiform discharge (IED). Experiments in primates demonstrate higher correlation coefficients between LFP and BOLD versus MUA and BOLD implying that overall, the synaptic input in a region is a greater determinant of BOLD signal than synaptic output, although MUA and BOLD are still correlated albeit at a lower level (Logothetis 2008). Neural and BOLD responses are also noisy and even neural responses may become decoupled over some circumstances e.g. when a neural response becomes adapted. Task-related BOLD appears to remain coupled to
LFPs, in the gamma frequency range even if the neural responses are dissociated and the strength of coupling is correlated with increased synchronicity (Niessing, Ebisch et al. 2005). Similarly negative BOLD responses have been found to be correlated with decrease in LFPs (Shmuel, Augath et al. 2006).

2.12.6 Neurovascular coupling: the basis of the BOLD signal

The observation that BOLD signal increases are related to higher concentrations of deoxyhaemoglobin is counterintuitive, given the relationship with the T2* imaging discussed above. In fact there is a mismatch between a compensatory increase in local cerebral blood flow (CBF) and the increase in regional cerebral oxidative metabolism (CMRO₂) related to tasks (Fox and Raichle 1986) and it is this mismatch which results in the increase in task related regional increased BOLD signal, observed in early fMRI experiments.

There is evidence that the majority (85%) of energy consumption with the brain is associated with neural activity (Jueptner and Weiller 1995) and this is predominantly accounted for by pre rather than post-synaptic mechanisms. In addition evidence from microinjection of neurotransmitters suggests that cerebral blood flow is regulated by glutamate and GABA (Yang and Iadecola 1996). Taken together, this suggests that BOLD signal, which reflects changes in CBF and CMRO₂ as discussed above, is an accurate representation of neural activity rather than another effect in the brain (Logothetis and Pfeuffer 2004) although the relationship is indirect and is still not fully evaluated.
2.12.7 Measuring and Interpreting BOLD Signal Change: principles of fMRI experiments

Simultaneous electrophysiological and fMRI experiments in primates have allowed detailed evaluation of the relationship of haemodynamic changes to neurophysiological events in normal physiological events, resulting in the conclusion that BOLD reflects neuronal activity and specifically pre-synaptic activity as discussed above. There has also been focus on describing the timing and dynamics of the BOLD signal change following neural stimulus which is referred to the ‘haemodynamic response function’ and in humans peaks 6-9 seconds following the stimulus in any given region and follows a typical shape (Figure 2.2).

![Figure 2-2 Typical Haemodynamic response function](image)

The general approach to fMRI analysis, therefore is to use a stimulus or task (which may be a single event or ‘block’) interspersed with periods of baseline or rest. The timecourse of the stimuli or tasks is then convolved with the canonical HRF as
described above in a general linear model (GLM) over each voxel in the brain resulting in a map of brain regions in which the BOLD signal follows the timecourse as the task-related neural activity.

2.12.8 fMRI applied to Epilepsy

fMRI has been used to aid planning of neurosurgical procedures for many years particularly in neuro-oncology, for example mapping primary motor cortex to guide the resection of tumours. Recently, the advent of ‘real time’ fMRI and the use of automated techniques incorporated into scanners has allowed many more centres to use the approach to accurately map resection zones with the aim of replacing intraoperative cortical stimulation or ECOG (electrocorticography). It must be born in mind, however, that there are differences in the resolution, the effects of brain shift and other inaccuracies (Nimsky, Ganslandt et al. 2000), meaning pre-operative fMRI may not be entirely reliable to guide resection and that experience and expertise is required in order to utilise it effectively.

In Epilepsy surgery, the role of cognitive and task related fMRI studies has been two-fold. Firstly to aid resection mapping as described above, and also at the group level to study the neurobiology of epilepsy and in particular the way in which functional cerebral networks are altered in the condition. This is particularly relevant in the study of language and memory function in relation to mesial TLE.

2.12.8.1 Language fMRI in epilepsy

Language fMRI is an established technique which is relatively simple to perform, and follows a block design during which a subject is presented with a visual stimulus and a related language task (e.g. generation of a verb associated with a noun appearing on a
screen) followed by a ‘rest period’ during which the subject is required to fixate a target, but not perform a task.

The tasks used are designed to selectively activate expressive language areas, typically the left inferior frontal gyrus (Broca’s area), while reading tasks tend to involve more superior temporal regions in addition. Even in left handed subjects, it is unusual to have right sided or bilateral areas activated during language tasks. The tasks have been extensively evaluated and have been found to have inter-subject reliability, both in controls and various patient groups, although frontal activations are generally more reliable than temporo-parietal areas. The potential of the technique to accurately and non-invasively identify language areas is tantalising, but in reality it can be difficult to discern whether a region of active brain is activated as part of the essential language network or whether it is in fact a non-essential accompaniment.

2.12.8.2 Application in Temporal lobe epilepsy

There are now around 30 studies which compare language fMRI with the intracarotid amytal test (IAT), with the aim that language fMRI should replace this invasive approach to the pre-surgical lateralisation of language in patients undergoing temporal lobectomy (reviewed in (Abou-Khalil 2007)). It is difficult to compare these studies owing to variability in both the IAT and fMRI paradigms, but the effects are considered to be reproducible and the IAT is increasingly not used in many centres for this purpose (Powell and Duncan 2005).

The reliability of language lateralisation has recently been shown to be improved by using a battery of cognitive tests rather than a single approach and one study has shown this approach to have more reliable concordance with the IAT. It should be understood that such tests can be affected by the fact that the most subjects have left
lateralised language and therefore the pre-test probability will be of a left sided result – there are attempts to account for this as truly useful clinical language fMRI needs to be able to lateralise above and beyond pre-test probability (Medina, Bernal et al. 2007).

Post-operative studies are beginning to emerge now and show that pre-operative language fMRI may be able to contribute to predicting post-operative memory decline (Binder 2010).

In addition to the obvious application in lateralising language prior to surgery, fMRI has also been used to study language networks in different epilepsy syndromes (Rutten, Ramsey et al. 2002, Gaillard, Balsamo et al. 2004), for example in both left temporal lobe epilepsy and benign epilepsy patients were less likely to have left lateralised language compared with controls (Weber, Wellmer et al. 2006) (Yuan, Szafarski et al. 2006) while abnormalities of language lateralisation are also reported in patients with other left hemisphere epilepsies.

The observation that alteration in language function (shifting from left to right hemispheres) correlated with spike frequency in patients with left mesial TLE suggests that language fMRI might be a useful tool to investigate dynamic changes in cognitive networks in patients with epilepsy (Janszky, Mertens et al. 2006) (e.g. transient cognitive impairment associated with interictal spikes in children with BECTS (Binnie and Marston 1992)).

Altered functional connectivity in language networks has also been reported in temporal lobe epilepsy using fMRI, which will be discussed briefly in section 2.14.
2.12.9 Memory fMRI

It is likely that work to implement fMRI of memory functions will produce a clinically relevant tool for assessment of memory fairly soon, similar to that which is used to assess language although clinical validation of such an fMRI protocol will be challenging given the complexity of memory tasks.

2.12.9.1 Memory fMRI in Temporal Lobe Epilepsy

The study of memory using fMRI is more complex than language function, partly as the protocols used are more variable and it is difficult to develop reliable in scanner methods of assessing memory. In general the design of tasks is reliant on measuring changes with the mesial temporal lobe structures when viewing pictures or words which are to be memorised; it is assumed that the BOLD signal change observed in these regions represents neural activity related to memory encoding. One particular challenge, is that, as mentioned earlier, EPI signal dropout is particularly problematic in the mesial temporal lobes, meaning that the area may be less sensitive to BOLD signal change.

In general, studies using memory fMRI have shown that there is reduced BOLD signal change in the affected side in patients with TLE when testing verbal memory (Richardson, Strange et al. 2003), and that there is evidence of reorganisation of memory networks in patients with TLE compared with controls with lateralisation of memory affected by the side of seizure onset. As well as brain activity in mesial TL regions, memory fMRI tasks tend to show activity also in frontal lobe regions.

In practical terms, similar to language, the most attractive use of memory fMRI would be as a predictive tool for post-operative memory decline in patients undergoing
temporal lobe resection. Several studies have approached this issue in the last
decade, initially separated into non-verbal and verbal memory tasks, both of which
showed that greater residual function in the ipsilateral mesial temporal structures to
seizure onset was predictive of greater post-operative memory decline (i.e. more left
lateralised subjects with intact verbal memory, would have a worse outcome than those
in whom memory was more bilateral/right localised while the converse is true for visuo-
spatial memory, suggesting 'the more you have, the more you may lose') (Richardson,
Strange et al. 2006, Powell, Richardson et al. 2007, Powell, Richardson et al. 2008)
both at the group level and in small numbers of individual patients. A large cohort
study, combining multiple verbal and non-verbal memory has been carried out in
patients with right and left TLE, which confirmed the observation that greater fMRI
activation in the ipsilateral medial temporal lobe structures was correlated with a
greater post-operative memory decline following resection of the temporal lobe,
although the effect was more marked for verbal memory in left TLE than visuo-spatial
memory in right TLE (Bonelli, Powell et al. 2010). The authors were also able to
demonstrate, however, that differences in activation patterns in the anterior and
posterior hippocampus may also have some predictive value for post-operative
memory function. A further study showed differences in the way post-operative
remodelling memory occurs in left vs right anterior temporal lobe resection (reflecting
verbal and visual memory respectively) and specifically that following left anterior
temporal lobe resection, post-operative verbal memory performance relates to pre-
operative reorganisation of memory function rather than post-operative hippocampal
reserve (Bonelli, Thompson et al. 2013). Similarly pre-operative recruitment of more
extensive networks in memory encoding (including extra-temporal regions) in patients
with both right and left hippocampal sclerosis is also associated with better memory
outcomes (Sidhu, Stretton et al. 2013). These studies, which have produced reproducible results in increasingly large numbers of patients suggest, that despite the difficulties in establishing good quality fMRI paradigms for the study of memory, that clinical use of memory fMRI for predictive purposes in epilepsy surgery is promising.

A further application of fMRI in patients with TLE arises from the observation that amygdale fMRI activation in response viewing fearful faces was found to contribute to seizure lateralisation in mesial TLE (Schacher, Haemmerle et al. 2006) while in patients undergoing right ATL, the degree of activation in the amygdale predictive with post-operative anxiety (Bonelli, Powell et al. 2009).

2.12.9.2 Cognitive fMRI in Frontal Lobe Epilepsy

While there have been fairly comprehensive imaging studies of cognitive networks in TLE, studies investigating those in FLE are much more limited. Patients with frontal lobe epilepsy are more heterogeneous than those with TLE and paradigms specifically addressing frontal lobe functions are difficult to develop (Centeno, Thompson et al. 2010); however it has been possible to demonstrate increased recruitment of cognitive networks in patients with frontal lobe epilepsy compared with normal controls during memory encoding (Centeno, Vollmar et al. 2012) and interestingly in patients with Juvenile myoclonic epilepsy there are abnormalities of frontal connectivity (specifically increased connectivity of motor and cognitive networks)(Vollmar, O’Muircheartaigh et al. 2011).

2.12.9.3 fMRI of motor function: integration in surgical systems

A major attraction of the evolving clinical role of functional MRI in epilepsy as well as neuro-oncology, is direct implementation of fMRI data into neuronavigation systems, to
enable image guided resection. The acquisition of fMRI data and subsequent implementation within these systems, however, raises a number of problems, primarily owing to mismatch between fMRI data which is acquired using fast T2* weighted imaging and suffers from both distortion and also signal dropout within certain brain regions as mentioned previously. While this can be overcome to some extent by coregistration with T1 weighted structural imaging, there is a further mismatch when surgery is attempted owing to the shift of cerebral structures when the skull is opened of up to 2cm (Nimsky, Ganslandt et al. 2000). Current work is attempting to overcome these difficulties by modelling the intracranial shift to allow integration of this data. The advent of intraoperative MRI is exciting and opens up the theoretical possibility of integrating fMRI data both prior to and during resection when awake craniotomy is not possible, although in practice, this is not likely to be feasible or safe for some time.

2.13 EEG fMRI

EEG-fMRI has been in use in research for two decades, during which time various developments in scanner technology, EEG equipment and computation, have made the technique easier to perform, meaning that more patients can be studied in a standardized way. There remain however, specific technical and safety considerations, which are discussed below. The initial motivation behind it use in epilepsy stemmed from the observation of IED-related BOLD signal change which was sometimes colocalised with regions giving rise to seizures, prompting the tantalizing promise of a new method to detect the seizure onset zone. The picture has subsequently been shown to be more complex, but fMRI remains a very attractive way to study both
interictal and ictal activity given that is non-invasive, has respectable temporal and spatial resolution and covers the whole brain.

2.13.1 Approach to simultaneous EEG-fMRI recording: Technical aspects

While the temporal resolution of EEG, MEG and icEEG is excellent, the spatial resolution is less good, even with the advent of high resolution EEG and in the case of icEEG spatial coverage is also necessarily limited by the number of electrodes which is it possible to implant (icEEG has a spatial resolution of 1cm$^3$), but the number of electrodes is limited by the local tissue damage and operative morbidity associated with icEEG. By contrast fMRI is limited in temporal resolution by the TR (in the order of seconds), but has better and improving spatial resolution limited only by voxel size (currently 2-4mm). The ability to combine both techniques, combining the temporal resolution of the former with the spatial resolution of the latter, is therefore a tempting proposition, although in reality, the two modalities, in fact measure different entities and the relationship between the two is complicated. Nevertheless, interesting results have been obtained over the last few years in this area, and the mechanisms underlying EEG-fMRI are increasingly well understood.

2.13.2 Technical considerations

2.13.2.1 Safety

During simultaneous EEG fMRI recordings, additional safety precautions are required compared to when the techniques are employed alone. This is because adverse effects can arise owing to induced currents flowing through loops or heating of EEG components in close proximity or contact with the subject, which theoretically may cause burns.
Safety of these experiments requires that non-ferrous material be used for electrodes and studies of safety and feasibility should ideally be carried out for each experimental set up as there are differences in both scanning and EEG equipment requiring different safety considerations.

One study recommended that one 10 kΩ current-limiting resistor be inserted serially at each electrode lead and the twisting of leads in a linear configuration being used to reduce the possibility of large (EEG lead-electrode-head-electrode-lead-amplifier circuit) loops. This was based on a worse case scenario for a 1.5T scanner. These recommendations have been incorporated into various commercial systems employing electrode caps with built in resistors. In a further study using and alternative EEG system, no significant heating was observed (Mirsattari, Lee et al. 2004). An important general consideration when placing wires in contact with the body is the type of RF transmit coil used and length of wire exposed to the electrical component of the field (Konings, Bartels et al. 2000). An illustration of a typical EEG-fMRI set up (from the same centre as the work presented here) is given below (Salek-Haddadi, Diehl et al. 2006).
Figure 2-3 Set up for EEG-fMRI experiments at the Epilepsy Society MRI Unit,

2.13.2.2 Safety in Intracranial EEG fMRI

The ability to record EEG-fMRI with depth electrodes in situ is tempting as it effectively removes some of the limitations of EEG fMRI, in particular the inverse solution applied to scalp EEG, which may result in multiple sources being identified, and poor spatial resolution. In order to better understand the neuronal substrates of BOLD signal particularly in epilepsy, it would be ideal to record EEG from depth electrodes in a known location and the correlated BOLD signal. In addition, the EEG is relatively free from physiological artifacts (e.g. muscle and eye movement), resulting in a theoretically highly specific model containing much more information than can be modelled with the standard EEG.
The safety considerations mentioned above all require additional consideration owing to the proximity of the depth electrodes to brain tissue when compared to scalp EEG. The initial problem of RF heating is one of the main considerations and various studies have been undertaken studying this in vivo with non-EEG devices (e.g., deep brain stimulators used in movement disorders). Once again each recording set up requires separate safety assessment, which leads to long and complex experiments, both to simulate the effects of the electrodes and EPI sequence on brain tissue and also, similarly in phantoms and animal models.

Initial work with both a physical gel phantom incorporating direct measurement of RF induced heating as well as simulations of the model have been undertaken recently (Carmichael, Thornton et al. 2008, Carmichael, Thornton et al. 2010) modelling a situation using depth and grid electrodes as would typically occur in a patient undergoing intracranial EEG recording. These studies found that the degree of heating observed was dependent on the SAR level (varying with the strength of magnet) and the arrangement of the electrodes and transmitting leads. Other centres have now also begun to explore this approach and have demonstrated the safety of their own protocols at 3T and 1.5T using a similar gel phantom approach (Boucousis, Beers et al. 2012).

Following these safety studies, the first in vivo studies of simultaneous intracranial EEG and fMRI (icEEG-fMRI), during the period in which this work was undertaken (Carmichael, Vulliemoz et al. 2012) (Boucousis, Beers et al. 2012, Cunningham, Goodyear et al. 2012) (Chaudhary 2013) (submitted) and Chapter 9.
2.13.2.3 Data Quality

If EEG is acquired by standard methods in the MRI scanner, in the majority of cases the signal becomes un-interpretable during image acquisition due to the presence of repetitive artefact waveforms superimposed on the physiological signal owing to the switching of gradients during EPI sequence acquisition (Anami, Mori et al. 2003) (Hoffmann, Jäger et al. 2000).

The first attempts at recording EEG inside MR scanners revealed the presence of significant pulse artefacts (so called BCG (ballistocardiogram artifact) (Sijbers, Michiels et al. 1999). This effect has been shown to be common across subjects (Sijbersa, Van Audekerke et al. 2000). The pulse artefact amplitude can reach 50 µV (at 1.5T) obscuring various features of the EEG and giving rise to difficulties in its interpretation. The precise mechanism through which the circulatory system exposed to a strong magnetic field gives rise to these artefacts remains uncertain, but it is thought to represent a combination of the motion of the electrodes and leads (induction) and the Hall effect (voltage induced by flow of conducting blood in proximity of electrodes). The wide field exhibited by the artifact on EEG would suggest that the effect would not be caused by movements of the leads relative to the head, but rather gross head movement resulting in a different area of scalp being perpendicular to the field (B0).

Measures to restrict movement of the head are employed in EEG-fMRI experiments such as the use of a vacuum cushion around the subject’s head and neck, but pulse artifact still occurs. Ives et al suggested that this might be due to the presence of small, pulse related movements which are not possible to control by external measures (e.g. Movement of blood within the aortic arch causing small movement of the thorax,
virtually invisible to the naked eye) (Ives, Warach et al. 1993). This effect is proportional to the scanner’s main field strength (Allen, Josephs et al. 2000).

In addition to artifacts on EEG, interaction between EEG and MRI systems results in artefacts caused by electrodes and leads on the images acquired (Ives, Warach et al. 1993) and this has affected the choice of EEG component materials (Benar, Aghakhani et al. 2003, Mirsattari, Lee et al. 2004, Negishi, Abildgaard et al. 2004, Niazy, Beckmann et al. 2005). Radio-frequency fields radiating from the EEG recording equipment placed in the vicinity of the scanner can cause severe image degradation and may therefore require shielding (Negishi, Pinus et al. 2007).

Different EEG-fMRI data acquisition strategies have been employed to minimize the impact of EEG artifacts.

a. Interleaved EEG-fMRI (Goldman, Stern et al. 2000, Bonmassar, Hadjikhani et al. 2001, Bonmassar, Schwartz et al. 2001). This method requires that there is a gap in the acquisition of fMRI where EEG features can be reliably observed and is most useful for studying evoked responses or slow variations in brain activity. The drawback of this is that EEG features of interest may be missed and therefore the yield may be lower than a continuous acquisition.

b. EEG-triggered fMRI. This involves the identification of EEG events online to trigger a burst of fMRI scanning, and prior to the advent of continuous acquisition, was of particular relevance to epilepsy research (Hoffmann, Jäger et al. 2000, Krakow, Lemieux et al. 2001)
c. Continuous EEG-fMRI acquisition which requires specially-designed amplifiers (with adequate dynamic range, bandwidth and sampling rate) enabling image acquisition artefact correction on- or off-line (Lemieux, Salek-Haddadi et al. 2001, Al-Asmi, Benar et al. 2003, Salek-Haddadi, Diehl et al. 2006).

2.13.2.4 Approaches to the Reduction and Correction of artefact on EEG

Methods to reduce gradient induced artifact on the EEG include both physical modifications to the acquisition method as well as post-processing and can be grouped as follows:

a. Reduction at source: Immobilisation and alignment of the EEG leads together with lead twisting and a vacuum cushion to minimise head movement (Goldman, Stern et al. 2000, Benar, Aghakhani et al. 2003)

b. Application of low pass filters in post-processing reduces some artefact, although this alone is not sufficient to enable accurate identification of events on the EEG (Allen, Josephs et al. 2000)

c. Use of procedure specific MR sequences and effective synchronisation with the EEG (Goldman, Stern et al. 2000, Anami, Mori et al. 2003).

2.13.2.5 Reduction and Correction of the Image Acquisition Artifact

Filtering (Hoffmann, Jäger et al. 2000) template subtraction (Allen, Josephs et al. 2000) (Goldman, Stern et al. 2000) and/or ICA/PCA based methods have all been used to remove the image artifact following acquisition of the EEG.
Although filtering is reasonably effective, the most commonly used image acquisition EEG artefact reduction methods are based on average template artefact subtraction (AAS) method which enables the artifact to be separated from physiological signal by averaging the EEG over repeated epochs (based on the fMRI scanning rate). It relies on accurate knowledge of the timing of the scanner signal using sophisticated scanner-EEG synchronisation (Mandelkow, Halder et al. 2006). Continuous EEG-fMRI with good image artefact reduction was developed in house by the pioneering EEG-fMRI groups (Goldman, Stern et al. 2000, Krakow, Allen et al. 2000, Iannetti, Di Bonaventura et al. 2002), but is now available in commercial packages incorporating MRI-compatible hardware with automated image reduction programmes. Online EEG artefact subtraction has also been developed using a 250 Hz low pass filter in addition to artefact subtraction algorithms (Laufs, Kleinschmidt et al. 2003).

Possibly the most important practical development has been the demonstration that synchronised MR acquisition and EEG digitisation lead to significantly improved EEG quality, and in particular over a wider frequency range, when combined with an AAS-like method (Mandelkow, Halder et al. 2006)

2.13.2.6 Reduction and Correction of the Pulse Artifact

Correction of this artifact can be more problematic than the image acquisition artifact owing to beat-to-beat variability.

The standard artefact reduction algorithm is based on subtraction of a running average estimate of the artefact based on QRS complex detection, in principle similar to the method used to reduce imaging artefact (Allen, Polizzi et al. 1998).
Spatial EEG filtering methods have been proposed as an alternative means of correction based on temporal Principal Components Analysis (PCA) or Independent Components Analysis (ICA) (Benar, Aghakhani et al. 2003) (Otzenberger, Gounot et al. 2005) (Nakamura, Anami et al. 2006).

In addition to these post-processing methods, a recent study demonstrated that it was also possible to reduce artefact at source, similar to reducing the artefact on the images by immobilising the head to reduce the movement of vessels within the field and also the use of an insulating layer to reduce scalp motion related to small vessels in the head. Both methods were shown to be effective at reducing pulse artefact on the EEG (Mullinger, Havenhand et al. 2013).

Numerous refinements of the AAS and pulse artefact methods have been proposed using different approaches to improving the template (for example by employing independent or principal component analysis), or input parameters (e.g. subject position, head movement etc) (Negishi, Abildgaard et al. 2004, Debener, Strobel et al. 2007, Gonçalves, Pouvels et al. 2007, Masterton, Abbott et al. 2007, Laufs, Daunizeau et al. 2008, Mandelkow, Brandeis et al. 2010, Mullinger, Yan et al. 2011) (Ellingson, Liebenthal et al. 2004, Huiskamp 2005, Vincent, Larson-Prior et al. 2007, Ryali, Glover et al. 2009). Detailed discussion of all the refinements is beyond the scope of this review.

2.13.2.7 Additional regressors and new developments in analysis

On of the difficulties with interpreting EEG-fMRI is that there one is attempting to explain variance in the fMRI signal by examining the EEG, and this is necessarily limited if one has not adequately controlled for variance explained by other variables. This has led to investigation of other physiological variables using simultaneous
synchronized video EEG-fMRI such that respiration and eye blinks can be included in the model improving sensitivity and specificity (Chaudhary, Kokkinos et al. 2010, Chaudhary, Rodionov et al. 2012). There is also potential to incorporate normal features of the EEG such as sleep state (Moehring, Moeller et al. 2008).

Recently, EEG-fMRI in high field scanners has been implemented in some centres (Neuner, Warbrick et al. 2013).

2.13.3 Summary: technical aspects

In summary, since the first recordings of simultaneous EEG-fMRI, the technique is now relatively easy to perform with specifically designed commercial systems. Improvements in data quality and technical advances continue to evolve to the point that synchronized video EEG-fMRI and simultaneous intracranial EEG-fMRI are now technically possible and safe, opening new avenues for research and clinical application.

2.13.4 EEG-fMRI applied to Epilepsy

The study of the haemodynamic correlates of pathological EEG patterns observed in epilepsy by use of EEG-fMRI has developed since the mid-1990s and indeed provided the original impetus for this development. In addition to the attraction of recording EEG in the MR scanner to allow the study of individual interictal discharges, the initial motivation for combining the two modalities was to overcome some of the deficiencies in each technique, in particular the problem of EEG source localisation (the inverse solution) and the low temporal resolution of fMRI by combining the two modalities although, as has been alluded to above, combining both techniques, does not necessarily result in a reduction of the limitations of either.
Despite the methodological challenges encountered in implementing the technique, results obtained from early studies suggest that it has promise; both to provide a new form of localising information in patients with epilepsy as well as proving a useful technique to explore the physiology of interictal epileptic events and more recently, seizures. The work presented here also adds to the existing evidence that it may play some role in pre-surgical evaluation.

2.13.4.1 IED related BOLD changes in focal epilepsy: approaches to analysis

The aim of establishing EEG-fMRI in the first instance was to infer the location of irritative and seizure onset zones, with the hope of providing useful clinical information particularly in patients undergoing pre-surgical evaluation.

Using an IED (interictal epileptic discharge) triggered technique, whereby images were only acquired following the observation of an EEG event of interest and compared voxel-by-voxel to images acquired following periods of background EEG, initial studies in selected patients with focal epilepsy revealed significant BOLD increases in an large proportion of cases although the statistical tests applied varied widely. It should be noted that early studies focused on the identification of BOLD signal increases, neglecting the possibility of BOLD decreases, which were subsequently shown to be of considerable interest.

The continuous EEG-fMRI acquisition approach was made possible by the use of EEG processing methods to correct scanning-related artefact (Lemieux, Salek-Haddadi et al. 2001). The analysis of this type of data requires the creation of a model of the BOLD signal over the entire experiment by identifying images that coincide with EEG events of interest, such as IED. This model is then used to find voxels with BOLD
signal time courses using correlation. The identification of the events of interest is usually made by human observers and suffers from the well-documented limitations of this approach (Salek-Haddadi, Diehl et al. 2006) and a recent investigation into this issue, suggests that inaccurate labelling of EEG events can result in significant variation in the resulting maps of BOLD signal change. In addition to the limits of an observer derived EEG model per se, not all patients will have IEDs in the scanner presenting a further difficulty. In the two largest case series of continuously recorded EEG-fMRI in focal epilepsy around 50% of patients had IEDs during scanning. Approximately 60% of these had a BOLD signal change recorded in the vicinity of the electroclinical localisation of seizure onset (known as concordant BOLD signal change). Table 2-8 summarises the findings of EEG-fMRI studies in focal epilepsy. This figure represents the ‘yield’ of EEG-fMRI in a given study.

It is improved by modelling runs of IEDs rather than single events in addition to improvement in the EEG model by adequate spike detection and classification by the observer (Liston, De Munck et al. 2006). Further improvements in yield have been investigated in work performed in the context of this thesis in conjunction with colleagues at the Epilepsy Society and in Geneva which are discussed in more detail in the discussion sections which follow each experiment (Vulliemoz, Rodionov et al. 2009, Vulliemoz, Thornton et al. 2009, Grouiller, Thornton et al. 2011).
Table 2.8 Summary of the results of EEG-fMRI studies comparing BOLD signal change with electroclinical localisation of seizures

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warach et al 1996</td>
<td>1</td>
<td>Bilateral increase in BOLD signal</td>
<td>First case report of IED related BOLD signal change</td>
</tr>
<tr>
<td>Seeck et al 1998</td>
<td>1</td>
<td>Multiple areas including SOZ</td>
<td>First case combining 3d-source localisation with EEG-fMRI</td>
</tr>
<tr>
<td>Symms et al 1999</td>
<td>1</td>
<td>Concordant increase in BOLD</td>
<td>First study demonstrating reproducibility</td>
</tr>
<tr>
<td>Patel et al 1999</td>
<td>20</td>
<td>10 had IEDs. 9/10 had activation corresponding to EEG focus</td>
<td></td>
</tr>
<tr>
<td>Krakow et al 1999</td>
<td>10</td>
<td>Reproducible activations concordant with EEG focus in 6/10</td>
<td></td>
</tr>
<tr>
<td>Krakow et al 1999</td>
<td>1</td>
<td>Focal activation in large MCD</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Observations</td>
<td>Key Points</td>
</tr>
<tr>
<td>------------------------</td>
<td>----</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lazeyras et al 2000</td>
<td>11</td>
<td>Activation concordant with clinical localisation in 7/11. 6 had icEEG (concordant in 5/6)</td>
<td>First series comparing with icEEG</td>
</tr>
<tr>
<td>Krakow et al 2001</td>
<td>24</td>
<td>14 with IEDs, 12 concordant with EEG focus, 2 discordant.</td>
<td></td>
</tr>
<tr>
<td>Lemieux et al 2001</td>
<td>1</td>
<td>IED-relate BOLD concordant with electro-clinical focus</td>
<td>First description of continuous acquisition</td>
</tr>
<tr>
<td>Jager et al 2002</td>
<td>10</td>
<td>5 IEDs, focal activation in all</td>
<td>Use of EEG amplitude as a repressor to improve sensitivity</td>
</tr>
<tr>
<td>Al-Asmi</td>
<td>48</td>
<td>31 IEDs, IED-related BOLD in 39% of studies. Concordant icEEG in 4 patients</td>
<td></td>
</tr>
<tr>
<td>Benar et al 2006</td>
<td>5</td>
<td>5/5 had icEEG with IZ close to at least one region of activation in all.</td>
<td>First systematic comparison with icEEG (patients reported elsewhere)</td>
</tr>
<tr>
<td>Aghakhani et al 2006</td>
<td>64</td>
<td>40 with IEDs. Thalamic response in 12.5% unilateral IEDs and 55% with bilateral.</td>
<td>Early report of sub-cortical involvement in focal epilepsy</td>
</tr>
<tr>
<td>Salek-Haddadi et</td>
<td>63</td>
<td>40 IEDs, Concordant BOLD signal change in 68% of patients,</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Findings</td>
<td>Context</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>al 2006</td>
<td></td>
<td>activation more concordant than deactivation</td>
<td></td>
</tr>
<tr>
<td>De Tiege 2007</td>
<td>6</td>
<td>4/6 IED related BOLD signal change concordant with seizure onset</td>
<td>First systematic study in children</td>
</tr>
<tr>
<td>Zijlmans et al 2007</td>
<td>29</td>
<td>15 had IEDs, 4 had concordant IED related BOLD signal change</td>
<td>First study investigating EEG-fMRI in pre-surgical evaluation</td>
</tr>
<tr>
<td>Thornton et al 2010</td>
<td>23</td>
<td>10 had IEDs and post operative data. 6 concordant with resected region, had good outcome.</td>
<td>First study of EEG-fMRI and post-operative outcome</td>
</tr>
<tr>
<td>Grouiller et al 2011</td>
<td>23</td>
<td>Novel analysis of EEG showed BOLD signal change in 14/18 patients who with 'inconclusive' conventional analysis</td>
<td>Largest series comparing IED-related BOLD signal change with icEEG.</td>
</tr>
<tr>
<td>Thornton et al 2011</td>
<td>23</td>
<td>12 with IEDs, 11 with IED-related BOLD. Widespread BOLD associated with poor outcome</td>
<td></td>
</tr>
<tr>
<td>Pittau 2012</td>
<td>43</td>
<td>33 with IEDs, 29 with concordant BOLD response, 21 with 'contributory BOLD response'</td>
<td></td>
</tr>
<tr>
<td>Van Houdt et al 2013</td>
<td>16</td>
<td>76% of regions IED related BOLD concordant with active icEEG electrodes. Unrelated to post op outcome</td>
<td></td>
</tr>
</tbody>
</table>
2.13.4.2 The BOLD response in EEG-fMRI

The BOLD response is complex and there is commonly IED-correlated BOLD signal change observed remote from the EZ and IZ as well as in close proximity to the seizure onset zone, with regions of BOLD decrease often observed at remote sites. The interpretation of these remote changes remains one of the active areas in EEG-fMRI research and investigations into this have included comparison with electrical source localisation (discussed below) as well as studies of the haemodynamic response.

As a general rule, previous studies suggest that the time course of the BOLD increases related to focal spikes is similar to that observed following brief stimuli in healthy subjects (Friston, Frith et al. 1995), peaking at 5-6 seconds after the stimulus and returning to baseline roughly 15 seconds later. This is the so-called canonical haemodynamic response function (HRF).

Deviations from the normal time course, however, have been observed in epilepsy. While the BOLD response, both positive and negative, to external stimuli has been studied extensively with reference to neuronal activity in healthy subjects, there have been suggestions that this relationship may be altered in the case of interictal epileptiform discharges. A formal study investigating this possibility found that the inclusion of non-canonical time courses does not lead to an important increase in yield (Salek-Haddadi, Diehl et al. 2006). More recent studies suggest non-canonical HRFs associated with IEDs are often remote from the presumed seizure onset zone, but whether this represents artefact, propagation of epileptiform activity (time-locked activity) or another phenomenon was not clear (Lemieux, Laufs et al. 2008). In addition, an investigation combining perfusion studies and EEG-fMRI in generalised
spike and wave discharges showed that cerebral blood flow and BOLD signal change were correlated, suggesting that coupling is preserved in this situation.

Some researchers have emphasised the importance of intersubject variability in the HRF and routinely use ‘individualised HRFs’ in the analysis of IED correlated fMRI (Benar, Gross et al. 2002, Bagshaw, Aghakhani et al. 2004, Gotman 2008) and the issue is still under debate. Variability in the HRF in the developing brain has been suggested by Jacobs and colleagues who demonstrated that the HRF was longer in children under 2 years, compared with older patients (Jacobs, Hawco et al. 2008).

Early BOLD signal change (time locked to IEDs) has been reported in focal epilepsy (Hawco, Bagshaw et al. 2007, Lemieux, Laufs et al. 2008) and there has also been BOLD activation reported prior to the onset of Generalised spike and wave discharges (Moeller, Siebner et al. 2008). It seems most likely that these reflect neuronal activity preceding an event observed on the scalp. An investigation specifically evaluating IED related BOLD decreases hypothesised that there should be early response seen prior to the event (i.e. the decrease represented a ‘late response’ to an event not seen on scalp EEG), however, and did not find that this was the case (Rathakrishnan, Moeller et al. 2010). The same group also examined non-simultaneous icEEG data to find if there were abnormalities on icEEG which might account for early BOLD responses, but only found changes in one patient (Pittau, Levan et al. 2011).

Another explanation for these early responses suggested that they occurred owing to disrupted neurovascular coupling, but an investigation of the relationship between blood perfusion and BOLD changes linked to epileptiform discharges in focal (one case) and generalised epilepsies, are consistent with preservation of neuro-vascular coupling in epilepsy (Carmichael, Hamandi et al. 2008, Hamandi, Laufs et al. 2008).
Interestingly, one experiment reported the occurrence of BOLD signal abnormalities even preceding the development of epileptic spikes in an animal model following penicillin insult (Makiranta, Ruohonen et al. 2005).

2.13.4.3 Localisation of BOLD changes in focal epilepsy

IED correlated BOLD signal change may be co-localised with the irritative or epileptogenic zones (IZ, EZ), and there have been efforts to validate EEG-fMRI localisation by comparison with other non-invasive localisation methods and the gold standard of intracranial recording (see table 2-8 for a summary of relevant studies). There have been reports, predominantly within larger series, of ‘concordance’ of IED correlated BOLD response with seizure onset identified by intracranial recording (Lazeyras, Blanke et al. 2000, Bagshaw, Kobayashi et al. 2006, Salek-Haddadi, Diehl et al. 2006, De Tiege, Laufs et al. 2007) but the only more systematic study was limited to a 5 case series at the time the experimental work in this thesis was undertaken. Here it was found that where EEG fMRI activations were identified, there was at least one active electrode on intracranial recording in the same location. The same series made a comparison with source analysis from standard scalp EEG (Benar, Grova et al. 2006).

Comparison of non-invasive distributed EEG source localisation and EEG-fMRI activations have been made using both spike-triggered fMRI and continuous acquisition. An initial study observed that dipolar source localisation was often remote from EEG-fMRI localisation (Lemieux, Krakow et al. 2001) while a recent systematic study using calculated measurements over the cortex revealed IED-associated BOLD clusters which were highly concordant with distributed sources in most patients studies, but also that other EEG-fMRI sources were present which were not concordant with the
distributed sources (Grova, Daunizeau et al. 2008). A paediatric study looking specifically at Benign Epilepsy with centro-temporal spikes showed EEG-fMRI activations concordant with Multiple source analysis in 3 out of 4 patients studied (Boor, Jacobs et al. 2007). Further studies undertaken by our group during the course of this thesis alongside collaborators working with paediatric patients have shown that high quality electrical source imaging can be undertaken on EEG recorded during fMRI and can be used to inform the interpretation of IED-related BOLD signal change, by separating onset from propagation of spikes (Groening, Brodbeck et al. 2009, Vulliemoz, Lemieux et al. 2009).

Other methods of using the EEG to inform the interpretation of IED-related BOLD signal change are now being developed, particularly with the aim of improving the yield of the technique, and there have also been investigations into the accuracy with which EEG events are detected and modelled. These are discussed further in the context of the experimental work to which they relate.

### 2.13.4.4 EEG fMRI in Pre-surgical Evaluation of Focal Epilepsy

Comparison of novel localisation techniques in focal epilepsy with intracranial EEG, the current gold standard, is considered the best method for validation, and has been used in EEG-fMRI as described above. However, it has drawbacks. Intracranial EEG records directly from regions of interest, but has reduced spatial coverage owing to the limited number of electrodes which can be implanted. The problem of source reconstruction found in scalp EEG is not abolished as many regions of interest cannot be accurately sampled using current methods. Nevertheless, it remains one of the best methods of identifying the likely irritative and epileptogenic zones before resection.
Only one group had specifically addressed the use of EEG-fMRI in surgical planning (Zijlmans, Huiskamp et al. 2007), at the time that this work was commenced, carrying out studies in a group of 29 patients previously rejected for surgery with frequent IEDs. They reported useful EEG-fMRI results in 6 patients, 4 of whom proceeded to surgical resection and suggested that EEG-fMRI may contribute to the surgical decision making process when standard methods did not identify a surgical target. Further data is now beginning to emerge which is discussed in chapter 10 and 11 (van Houdt, de Munck et al.) (Donaire, Capdevila et al. 2013).

2.13.4.5 BOLD changes associated with specific pathologies in focal epilepsy

In lesional epilepsy it is known that the IZ and EZ may extend beyond the anatomical boundary of pathological abnormality and in addition, both in vitro and animal models suggest abnormal sub-populations of neurones within dysplastic areas (Najm, Tilelli et al. 2007). EEG-fMRI has therefore been used as a tool to evaluate the haemodynamic response in areas of cortical malformation and other pathologies (Krakow, Woermann et al. 1999, Federico, Archer et al. 2005, Kobayashi, Bagshaw et al. 2005).

In general, EEG-fMRI studies of malformations of cortical development have shown variability in BOLD response within pathologically abnormal regions with broadly concordant activations reported in both grey matter heterotopia (Kobayashi, Bagshaw et al. 2006) and focal cortical dysplasia (Federico, Archer et al. 2005). In both these studies, BOLD decreases were observed remote to the area of pathological abnormality. Other studies of MCD have supported these findings including those in icEEG and the findings lend support to the view that cortical dysplasia is often a multifocal disease (Aubert, Wendling et al. 2009, Fauser, Sisodiya et al. 2009).
Understanding of the epileptic networks involved in FCD is important as FCD is a common pathology in patients with seemingly normal MRI (McGonigal, Bartolomei et al. 2007) and in addition, the findings of dysplastic tissue outside of the region of resection is associated with poor surgical outcome (Fauser, Schulze-Bonhage et al. 2004). We were therefore interested in whether the patterns of IED-related BOLD signal change corresponded to abnormalities on icEEG in this group of patients. Our findings are presented in chapter 6.

The frequent IED-related BOLD decreases, particularly in MCD, have been attributed to loss of neuronal inhibition (in the presence of normal neurovascular coupling) in the regions surrounding the abnormality or abnormalities in neurovascular coupling itself. The significance of these deactivations will be discussed in more detail below.

A recent study of IED-related BOLD signal change in cavernomas (Kobayashi, Bagshaw et al. 2007) suggested BOLD signal change both within the area of anatomical abnormality and within areas remote to it. Caution is required in interpreting BOLD signal change in these very vascular lesions as T2* sequences used in EEG-fMRI are very sensitive to haemosiderin within the lesions.

EEG-fMRI results in tuberous sclerosis reflect similar pattern. In a recent study exclusively investigating paediatric patients, it was found that BOLD activation was variable between tubers and extended beyond the border of tubers as identified on structural images once again supporting the view that EEG fMRI may be a useful technique in assessing the epileptic network beyond areas of structural abnormality (Jacobs, Rohr et al. 2008).
2.13.4.6 EEG-fMRI and the paediatric epilepsies

The paediatric population have been generally less well studied with EEG-fMRI than adults (although some of the studies above have included several children). The experiments are lengthy and can be difficult to tolerate particularly as they require subjects to remain still for the duration of the procedure. However, intracranial recording is also difficult in children and invasive procedures such as this may be less acceptable to the paediatric population meaning that the need for development of non-invasive techniques for localization of the seizure onset zone is even more pressing.

There have been several series using EEG fMRI in groups of children with focal epilepsies of mixed aetiology illustrating that the experiments are tolerated and results may also show concordance with the seizure onset zone (De Tiege, Laufs et al. 2007). In the most recent of these studies it has been found that deactivations are more common and more widespread than in adults all although a common pattern was not identified in this group (Jacobs, Kobayashi et al. 2007). Questions remain regarding whether this is a function of age and the developing brain, of the particular epilepsy syndrome under study, or whether it in fact related to pharmacological sedation, the use of which is necessary in children undergoing EEG-fMRI. An investigation into the BOLD response at different ages showed that BOLD responses were generally longer in children under 2 also commented that high spiking rates often present in childhood epilepsies may affect the HRF (Jacobs, Hawco et al. 2008). Previous studies have suggested that Benzodiazepine sedation may affect BOLD response to IEDs (Ricci, De Carli et al. 2004).

Specific syndromes are now being studied in children. Two groups of children with BECTS have undergone EEG-fMRI and both studies reported BOLD signal change
concordant with the electroclinical localisation (Boor, Jacobs et al. 2007). (Lengler, Kafadar et al. 2007). More recently an interesting case series has demonstrated variability in IED-associated BOLD signal change in children with Dravet syndrome, despite the same underlying gene defect (SCN1A mutation) (Moehring, von Spiczak et al. 2013).

2.13.4.7 EEG-fMRI in generalised epilepsy

In generalised epilepsy syndromes, EEG-fMRI has made a significant contribution to our understanding of the cortico-thalamic networks described in animal models (Avoli and Gloor 1982). Archer and colleagues were the first to report a pattern of BOLD decrease in the posterior cingulate and bilateral pre-central BOLD increase in relation to brief epochs of interictal generalised spike and wave discharges in 5 patients using triggered EEG-fMRI (Archer, Abbott et al. 2003), an observation which has been noted by other researchers (Aghakhani, Bagshaw et al. 2004, Hamandi, Salek-Haddadi et al. 2006, Moeller, Siebner et al. 2009) By grouping the results for cases with IGE on one hand and secondarily generalised epilepsy on the other, Hamandi et al were able to demonstrate that GSW is commonly associated with BOLD decreases in the precuneus/posterior cingulate and bilateral BOLD increases in the thalamus, and that there is considerable overlap between the patterns in the two groups.

The first studies of ictal haemodynamic changes were also recorded in generalised epilepsies – absence seizures were associated with a striking pattern of widespread cortical BOLD decrease and thalamic BOLD increase using continuous EEG-fMRI, consistent with a reduction of cortical activity during GSW and a key role for the thalamus (Salek-Haddadi, Lemieux et al. 2003).
The reproducibility of these patterns of BOLD signal change is striking and there is now much interest in evaluating the dynamics of these changes. Moeller and colleagues demonstrated early involvement of the precuneus and frontal cortex compared with thalamus in some, but not all patients studied with absence seizures (Moeller, LeVan et al. 2010), similar to animal models (David, Guillemain et al. 2008). Vaudano and colleagues found similar patterns and proposed a ‘gating’ role for the precuneus in GSW, such that the precuneus as a causal effect on the network (Vaudano, Laufs et al. 2009). EEG-fMRI thus emerges as a useful tool for studying this in humans; the particular clinical relevance being the identification of targets for possible therapeutic stimulation.

2.13.4.8 EEG-fMRI in the study the neurobiology of focal epilepsy

Aside from the observations regarding localization of the seizure onset zone in focal epilepsy, the observation of activations extending beyond the lesional zone in addition to deactivations (negative haemodynamic response) has led to attempts at exploring the ‘epileptic network’ using EEG fMRI in the resting state.

In focal epilepsy, initial investigations have focused on temporal lobe epilepsy, the most uniform and investigated syndrome. An initial series of 19 patients with temporal lobe epilepsy showed the majority had BOLD signal change in the affected temporal lobe, although the activations were usually neocortical (Kobayashi, Bagshaw et al. 2006). It should be noted that the temporal lobe is a difficult area with which to study IED-related BOLD signal change as the EPI sequences tend to have drop out in this region.

Given the observation the remote deactivations occur in temporal lobe epilepsy, a further study in a group of patients with Temporal lobe epilepsy showed that
deactivation of the precuneus is common and associated with activation in the
gsilateral hippocampus in relation to interictal temporal lobe spikes (Laufs, Hamandi et
al. 2007). This effect was not observed in a similarly selected extra temporal lobe
epilepsy group and was thought to reflect a suspension of the precuneus (a region
commonly activated in awake resting state in contrast to reduced conscious or task
states, and correlated with alpha activity on the EEG (Laufs, Kleinschmidt et al. 2003),
specifically in response to temporal lobe spikes. The authors pointed out that this may
reflect a sub-clinical suspension of the awake resting state analagous to the cortical
deactivation/ thalamic activation which occurs in response to GSW (generalised spike
and wave discharge)(Archer, Abbott et al. 2003). Recent research combining PET and
EEG-fMRI identified a single region involved in the epileptic network, regardless of the
syndrome, in patients with focal epilepsy analagous to similar regions described in
animal models (Laufs, Richardson et al. 2011) and suggesting that further group
analysis of this data may yield more interesting revelations about the behavior of the
network.

Methods to assess the functional and structural connectivity between activated regions,
such as dynamic causal modelling (Friston, Harrison et al. 2003) and diffusion tensor
imaging have recently been combined to investigate propagation of epileptiform activity
(Hamandi, Powell et al. 2008) and the continued evaluation of connectivity in the
epileptic network is an exciting area of evolving research. In the third section of this
project, we have explored functional connectivity further in EEG-fMRI data, by
comparing the dynamics of activation maps recorded using EEG fMRI with the patterns
of propagation in intracranial data using a non-linear analysis (chapter 8). Studies
related to this section are reviewed in more detail below.
These observations have paved the way for new experiments investigating the relationship between consciousness and epilepsy (Blumenfeld 2012) both in generalized and focal seizure syndromes and the increasing interest in acquiring ictal data will allow the evaluation of ever more complex networks.

2.13.4.9 EEG-fMRI of endogenous brain activity

Beyond the BOLD changes related to epilepsy-specific stereotypical discharges, such as focal interictal spikes, there had been limited study of other electrophysiological abnormalities. Inspired by methods employed in the study of the haemodynamic correlates of normal brain rhythms using EEG-fMRI (Laufs, Krakow et al. 2003, Mantini, Perrucci et al. 2007, Tyvaert, Levan et al. 2008). EEG frequency-band based approaches have been used to study patients with epilepsy, but these studies are restricted to case reports at present (Diehl, Salek-haddadi et al. 2003, Laufs, Hamandi et al. 2006). In the first of these delta power associated EEG-fMRI was correlated with the seizure onset zone as illustrated by intracranial recording. Further discussion of fMRI correlates of endogenous brain rhythms is reviewed in (Laufs 2008).

2.13.5 Evolving analysis methodology: interictal data

As we have seen, significant BOLD changes are not revealed in an important proportion of cases in which pathological EEG activity is observed during scanning. Methods designed to improve the sensitivity and specificity of EEG-fMRI include the use of automated approaches to spike detection and classification (Liston, De Munck et al. 2006) and more recently a more symmetric fusion of EEG and fMRI (Daunizeau, Grova et al. 2007).
A major limitation of EEG-fMRI is the lack of EEG abnormalities captured in a large proportion of cases studied, depending on the selection criteria. In such cases, the correlation approach cannot be used. This has lead to the exploration of data-driven (i.e. without reference to any other data) fMRI analysis in an attempt to identify patterns of BOLD signal specifically linked to the IZ and EZ, such as Temporal Cluster Analysis (TCA) and Independent Component Analysis (ICA)(Morgan, Price et al. 2004, Hamandi, Salek Haddadi et al. 2005, Rodionov, De Martino et al. 2007, LeVan and Gotman 2009).

What is clear from the discussion of EEG-fMRI in both endogenous brain activity and interictal epileptiform activity, is that the information from the EEG is only part of a jigsaw- all the studies discussed have found that there is variability in maps of BOLD signal change despite similar EEG features and conversely the same map of BOLD signal change can occur with different activity. This illustrates a fundamental flaw in these experiments- that we still do not understand the direct relationship between what we look at on the EEG and the haemodynamic response. In addition we continue to identify confounds and so the model remains imperfect. This has produced a great interest in devising fused models for EEG-fMRI analysis which combine information from both sources as well as attempts to define the relationship between scalp EEG and fMRI (the EEG transfer function)(Rosa, Daunizeau et al. 2010, Rosa, Kilner et al. 2010).

### 2.13.6 Ictal EEG-fMRI

Although EEG-fMRI has predominantly been used in the study of endogenous brain oscillations and interictal epileptic activity, it has allowed interesting insights into the behaviour of the epileptic network during seizures. Despite this attraction, the time for
each session is necessarily short, meaning capturing seizures during EEG-fMRI tends to have occurred by chance rather than design. In addition, clinical seizures result in additional safety concerns and are an additional source of motion which may complicate the analysis of any resulting data. Nevertheless, successful analysis of ictal fMRI as been possible since the advent of the technique.

Initial studies in focal epilepsy used clinical seizure onset as an event marker in fMRI studies without concomitant EEG, and noted an increase in BOLD signal time locked to or starting before the seizure and broadly localised with the site of seizure onset (Jackson, Connelly et al. 1994, Detre, Sirven et al. 1995, Federico, Abbott et al. 2005). The advent of simultaneous EEG-fMRI resulted in more sensitive detection of seizure activity allowing the development of EEG informed modelling of seizure activity as well as the recording of electrographic seizure activity (in which head motion is less of a problem). In most cases, the BOLD signal change was noted to be colocalised with, but more widespread than the seizure onset zone – an early case report in a patient with parietal lobe epilepsy and focal electrographic seizures demonstrated widespread intense BOLD signal change concordant with the site of seizure onset, which increased with cumulative numbers of seizures analysed (Kobayashi, Hawco et al. 2006). The authors also noted widespread deactivation on the contralateral side and in other areas of the brain. Following there have been more reports of ictal associated BOLD signal change, with similar findings (Di Bonaventura, Vaudano et al. 2006, Auer, Veto et al. 2008, Tyvaert, Hawco et al. 2008).
2.13.7 Modelling approaches to ictal data

2.13.7.1 Modification of the model input: identification of the seizure

Most investigators approached ictal EEG-fMRI using a classical EEG based GLM in the first instance, modelling the seizure with a single or series of box cars with on and offset corresponding to the beginning and end of the seizure. This approach has been taken in patients with both spontaneous and stimulus sensitive seizures (Kubota, Kikuchi et al. 2000, Iannetti, Di Bonaventura et al. 2002, Salek-Haddadi, Merschhemke et al. 2002, Kobayashi, Hawco et al. 2006, Tyvaert, Hawco et al. 2008, Marrosu, Barberini et al. 2009).

The approach, however does not allow for the evolution of ictal associated haemodynamic change over the timecourse of the seizure, and various approaches have been taken to allow for this.

Some studies have used serial fixed time windows over the time course to allow the observation of differential BOLD signal change beginning between 9 and 120 seconds prior to seizure onset on the EEG (Donaire, Falcon et al. 2009, Tyvaert, LeVan et al. 2009). Donaire and colleagues compared these changes with a baseline interictal period of 20 seconds, but not with the whole timecourse. This allowed differentiation of patterns of BOLD signal change during the course of the seizure, but the time windows chosen, although not arbitrary, were based on observations from alternative modalities including optical imaging (Suh, Ma et al. 2006) and did not make use of the available information on scalp EEG.

In the first of these studies focused on the haemodynamic changes within the ictal onset zone around the time of seizures, BOLD changes were mapped using GLMs
consisting of successive (and partly overlapping) short blocks modelling 10 second epochs of clinical events (Donaire, Bargallo et al. 2009). By applying series of contrasts across the successive blocks, different patterns of activation were revealed from 120 seconds before seizure onset and throughout the recorded seizures. However, as no baseline was modelled, the approach was limited to the illustration of what differed in terms of ictal haemodynamics within the seizure rather than what was ‘ictal’ about the pattern of activation overall. Similar results have been obtained in another study (Tyvaert, LeVan et al. 2009) which employed an analogous approach.

2.13.7.2 Flexible modelling of the BOLD response.

Another approach is to allow flexibility of the HRF when modelling seizures. While the canonical HRF has been demonstrated to be a suitable model in normal physiological conditions (Friston, Frith et al. 1995) and for IED-related BOLD signal change (Lemieux, Laufs et al. 2008), it has not been shown that it is the most appropriate model for ictal hemodynamic changes in humans. Evidence from optical imaging demonstrates that ictal haemodynamics vary both between subjects and also between seizures in a given subject showing a wide variety of temporal patterns (Zhao, Suh et al. 2007).

Salek-Haddadi and colleagues explored this with EEG-fMRI using a Fourier basis set (describing a set of sine and cosine functions) rather than a standard canonical HRF to allow for flexibility in the expected BOLD response to ictal activity in a single case. They demonstrated a peak BOLD response time-locked with EEG seizure onset and offset within the putative ictal onset zone (Salek-Haddadi, Merschhemke et al. 2002). A more restricted approach is to use multiple GLMs, with variable gamma functions allowing some flexibility in the time to peak of the HRF (Kobayashi, Hawco et al. 2006, Tyvaert, Hawco et al. 2008).
2.13.7.3 Recent studies of seizures

The evolution in understanding EEG-fMRI beyond simple identification of presumed epileptic foci, together with the technical ability and developing analysis approaches to ictal data has led to something of an explosion in the number of studies of seizures using fMRI including those reported above and case reports of reading epilepsy (Salek-Haddadi, Mayer et al. 2009, Vaudano, Carmichael et al. 2012), musicogenic epilepsy (Morocz, Karni et al. 2003, Marrosu, Barberini et al. 2009) and epilepsia partialis continua of the hand (Vaudano, Di Bonaventura et al. 2012) as well as fixation off sensitivity in generalized epilepsies (Iannetti, Di Bonaventura et al. 2002, Di Bonaventura, Vaudano et al. 2005, Moeller, Siebner et al. 2009).

2.13.7.4 Change in BOLD signal prior to seizure onset in focal epilepsy

A benefit of recording seizures has been the opportunity to observe pre-ictal changes in BOLD signal. It is well known that there in addition to the increased demand placed on cerebral metabolism and associated increase in cerebral blood flow, changes in both have been observed prior to the electro-clinical seizure onset on scalp EEG. PET and SPECT data suggest there are pre-ictal changes in cerebral metabolism and studies of cerebral blood flow support this (Baumgartner, Serles et al. 1998) while direct studies of optical imaging also show change in cerebral haemodynamics upto 20 seconds prior to seizure onset (Zhao, Suh et al. 2007). A fMRI study without simultaneous EEG in three patients suggested BOLD signal change may occur up to minutes prior to the electroclinical onset of focal seizures although in only one case, was this concordant with the seizure onset zone (Federico, Abbott et al. 2005). In other studies, widespread electrographic change was reported up to 30 seconds prior to seizure onset in focal epilepsy, with the initial change, concordant with the seizure...
onset zone (Donaire, Falcon et al. 2009). Using a similar approach, Tyveaert and colleagues noted ictal BOLD signal change generally starting 5.2+/− 2.6 seconds after electrographic seizure onset, but by relaxing the threshold some changes were noted prior to this (Tyvaert, LeVan et al. 2009). These findings are not surprising given the fact scalp EEG may be relatively insensitive to early ictal changes within deep structures (Nunez and Cutillo 1995) and there has been growing interest in the evaluation of these pre-ictal changes using a variety of different techniques. As has been discussed above, BOLD single change is associated with local field potentials in the gamma (or more) band and so it is perhaps not surprising that preictal changes are observed.

2.13.7.5 Data driven approaches to ictal EEG-fMRI

The drawbacks of the conventional GLM analysis have stimulated efforts to employ data-driven approaches that reduce the reliance on scalp EEG and increase sensitivity of the analysis. Exploratory attempts to analyse ictal fMRI data also suggested potential for data-driven approaches in this analysis (Detre, Sirven et al. 1995) leading to simulations studies of ICA applied to ictal data with promising results (LeVan and Gotman 2009) and we chose to explore this concept further by attempting to identify spatially independent components related to seizures and compare them with icEEG.

2.13.7.6 Independent Component Analysis: Theoretical considerations:

ICA is a method of signal processing which allows the separation of spatially or temporally independent components of a given signal, the classic example of this being the auditory processing of separate voices in a cocktail party scenario. Historically it has been applied to ‘noisy’ data sets as a method of improving signal to noise ratio including EEG, MEG and fMRI (Onton, Westerfield et al. 2006).
ICA aims to differentiate independent sources from a set of observed data, by assuming a mix of independent sources. It differs from PCA (principal component analysis which uncorrelates data from different sources while ICA achieves independence. Essentially PCA will demonstrate two or more uncorrelated variables, but it is possible to have two uncorrelated variables, which are not independent.

In fMRI, the method typically uses spatially independent components to 'unmix' compound signals recorded during scanning, which can subsequently be divided (by specific features) into signals arising from different sources.

ICA assumes that the source signals are not observable, statistically independent and non-Gaussian with an unknown, but linear mixing process. For any given signal, $X$ there are 'n' spatially independent components ($s_1, s_2, s_3, s_4...s_n$) each weighted by $A$ as follows:

$$X=As$$

The unknown matrix which mixes the signals is therefore $A_n$, and the process of ICA, results in an estimation of this matrix, $W$. Back transformation of this matrix results in an approximation of the spatially independent components, $y$.

$$y=WX$$

There are several approaches to the estimation of this matrix, the most frequently used of which use non-linear functions to generate algorithms to allow estimation of maximum likelihood and minimisation of mutual information. Constraints regarding the nature of the unmixing matrix, $W$, are applied.
2.13.7.7 Applications of ICA in fMRI

In fMRI data, the approach was first applied by McKeown and colleagues (McKeown, Makeig et al. 1998) and spatial ICA of fMRI data has now been used successfully to separate signals in visual and auditory experiments, identifying regions involved in perception that had similar timecourses to components in primary visual or auditory cortex (Castelo-Branco, Formisano et al. 2002, Zeki, Perry et al. 2003). In addition to the obvious application of ICA in ‘cleaning’ fMRI data of noise (for example motion), ICA is particularly applicable in the studying of resting state fMRI (rsfMRI) which is currently enjoying an explosion of interest in many different areas of research, both into cerebral physiology and pathology and there are numerous studies in which effects have been observed in resting state networks using ICA. One of the advantages of ICA is that it effectively provides a measure of ‘functional connectivity’, as any brain regions which contribute to a single component are, by definition, highly correlated. This observation has allowed the identification of networks in complex tasks (e.g. driving) for which it is difficult to model the fMRI data (Calhoun, Adalı et al. 2002). An obvious disadvantage in ICA, is that for a given dataset, it is possible to identify a large number of independent components with various different spatial patterns, meaning that although it is extremely sensitive, there is potential for significant observer bias in selecting components of interest. If a large enough number of components are identified, there is a high probability of identifying a component with a spatial pattern consistent with the effect of interest regardless of the source of that component.

Various methods have been used to validate identified components in fMRI of epilepsy including correlation with the timecourse of the events of interest (LeVan, Tyvaert et al. 2010, Moeller, Levan et al. 2010), or applying automated processes to the identification of component (De Martino, Gentile et al. 2007, Rodionov, De Martino et al. 2007).
2.13.8 Applications of data driven approaches to fMRI in Epilepsy

The first studies of seizures in fMRI were in effect ‘data driven’ or ‘model free’ ie they relied on the use of the fMRI signal alone, although the timing of the clinical seizure was known, allowing constraints to be placed on the points at which the fMRI time course should be studied.

Using this approach, early reports and case series demonstrated BOLD signal change in relation to seizures, modeling the seizure as a single block with onset and offset based on clinical observations (Detre, Sirven et al. 1995, Federico, Abbott et al. 2005). They commented that significant BOLD signal change around the region of cortex giving rise to seizures was observed in the period leading up to the seizure, but in the absence of a model for the fMRI data and advanced data-driven methods it was not possible to comment further on the nature of this signal change.

Other methods have subsequently been used to address the interpretation of fMRI signal change in the absence of events which can be modelled on EEG. Temporal clustering analysis (TCA) is one such approach which is essentially ‘model free’, though uses a mathematical tool to separate regions of interest where the BOLD signal changes in comparison with other areas (Morgan, Price et al. 2004) although this method is less sensitive when the same data is analysed with an EEG driven approach (Hamandi, Salek Haddadi et al. 2005).

2.13.9 ICA in EEG-fMRI.

In normal subjects ICA has demonstrated the presence and separation of the so called ‘resting state networks’ (RSNs) including the ‘default mode network (DMN) described by Raichle (Raichle and Snyder 2007) in fMRI data. These fMRI components were
shown to correlate with specific patterns in the EEG and it seems a logical extension of this that the principle should be applied in EEG-fMRI datasets in patients with epilepsy. Following this study, a correlation analysis has been undertaken for each of six of the ‘resting state networks’ recorded in EEG-fMRI experiments and separated using ICA of the fMRI data. Spectral analysis of simultaneously acquired EEG was undertaken and it was shown that each slowly fluctuating RSN was correlated with the power spectrum timecourse for a particular (much faster) EEG band (Mantini, Perrucci et al. 2007).

Following the observations that EEG timecourses could be specifically correlated with particular fMRI component timecourses, interest has grown in the application of the approach to epilepsy; specifically to answer the question ‘can epileptic components be identified using the approach?’.

To address this question, our group has studied ICA of fMRI in patients who had IED-correlated BOLD signal change using conventional GLM based analysis. An independent classifier was used to sub-divide the identified components in order to address the lack of specificity which is a common criticism in ICA. In a group of 8 patients with focal epilepsy, spatially independent components classified as likely ‘BOLD’ were identified which were spatially concordant with the result of the EEG driven model in each case. It was also demonstrated that the time course of the BOLD components correlated well with the time course of spikes recorded on EEG suggesting that ICA was an appropriate tool to investigate the BOLD signal in focal epilepsy at least for interictal epileptic discharges.(Rodionov, De Martino et al. 2007).

In another study, Levan and colleagues used independent component analysis in simulated datasets, demonstrating that it was possible to delineate the seizure onset
zone and also that the obtained components were stable in this data, corroborating the above findings (LeVan and Gotman 2009).

Following these experiments and given the success of data driven fMRI in early studies of seizure related BOLD signal change, ICA has subsequently been used to study ictal fMRI. Levan and colleagues reported a series of 10 patients who had seizure during scanning and ictal BOLD signal change using a General Linear Model based on the EEG (LeVan, Tyvaert et al. 2010). They then used ICA to decompose the fMRI signal and related the observed independent components to the regions of BOLD signal change identified using the general linear model and the electro-clinical features in each patient. The identified components were then deconvolved with a canonical HRF to verify their nature. One criticism of this approach is the observation that the results are to some extent, circular; i.e. if one deconvolves a component with the HRF, it will match the result of the GLM which is also derived by deconvolution of the HRF. At the same time as the work from LeVan and colleague, I undertook the study presented here in chapter 7.

More recently ICA has been used in the analysis of data from patients with IGE who also went standard event-related GLM analysis. The authors found that IED-related GLM analysis and ICA (components deconvolved with an ‘unrestricted HRF as above’ resulted in similar patterns of BOLD signal change. They concluded that ICA does not add information in cases where the GLM approach identifies regions of BOLD signal change (Moeller, Levan et al. 2010).

2.13.10 ICA of EEG in EEG-fMRI studies

In addition to ICA applies to fMRI, recent approaches have also applied ICA to EEG to improve artifact detection, in effect ‘cleaning’ the EEG by removal of those components
which relate to artefact. These have been used both in isolation for removal of pulse related artefact, but also in combination with existing template subtraction methods, although it controversial as to whether ICA adds to the standard method.

More recently work has focussed on using ICA in EEG to refine fMRI models. ICA has been used in analysis of scalp EEG to improve the detection of events (essentially ‘cleaning’ the EEG) following removal of artefact and also to separate EEG topography spatially concordant with IEDs. The approach, verified by epileptologists, was only carried out in cases with very frequent IEDs and IED-relate BOLD signal change allowing validation of the method (Marques, Rebola et al. 2009).

### 2.13.11 Application of ICA in this work

I used ICA to analyse fMRI data in patients in whom seizures were recorded, regardless of whether a GLM approach resulted in patterns of BOLD signal change. In order to improve specificity I used the same classifier as that used in our group’s previous interictal study rather than a deconvolution approach and correlated the component timecourse with the timecourse of the ictal changes on the scalp EEG.

### 2.14 Moving away from the ‘zone concept’ : Measures of Connectivity in Focal Epilepsy and their application in EEG-fMRI

The investigation of focal epilepsy has traditionally been based on the identification of discrete ‘zones’ as discussed above, corresponding to regions of cortex generating interictal discharges (IEDs) or ‘spikes’ (the irritative zone) and those regions which generate seizures (the seizure onset zone). There is a body of evidence, however, which suggests that although useful in the pre-surgical evaluation of epilepsy, this
understanding of focal epilepsy is simplistic and that there is a network of brain regions involved in the generation of seizures. Studies of particular epilepsy syndromes using stereoencephalography (sEEG) based on the methods pioneered by Bancaud and Talairach in the 1950s have identified many of these regions and measures of correlation in sEEG signals between regions involved in the irritative zone as well as those regions with ‘epileptogenic’ tissue have been used more recently to understand the way in which these networks are formed and behave (Wendling, Bartolomei et al. 2001, Aubert, Wendling et al. 2009, Bettus, Guedj et al. 2009) and further studies reviewed in (Wendling, Chauvel et al. 2010, Lemieux, Daunizeau et al. 2011).

EEG-fMRI offers the opportunity to extend this area of investigation as it benefits from whole brain coverage, while the increased understanding of the relationship between events recorded on EEG and associated haemodynamic responses allow inferences about neuronal activity to be made from the resulting BOLD signal changes.

It has been noted by many research studies that in addition to IED-related BOLD signal change co-localised with the seizure onset zone, additional clusters of IED-related BOLD signal change in close proximity as well as remote from the seizure onset zone are also revealed in most studies. The significance of these clusters has been investigated by various methods including group studies (in the case of temporal lobe epilepsy) (Laufs, Hamandi et al. 2007, Kobayashi, Grova et al. 2009) analysis of the haemodynamic response at sites of BOLD signal change lying remote from the seizure onset zone (Lemieux, Laufs et al. 2008) and more recently by combining EEG-fMRI with electrical source imaging (Groening, Brodbeck et al. 2009, Vulliemoz, Thornton et al. 2009).
Remote regions of BOLD signal change may occur owing to physiological phenomena (e.g. suspension of the resting state network related to generalised spike and wave discharges (Archer, Abbott et al. 2003, Hamandi, Salek-Haddadi et al. 2006)) or artifact, particularly when the response is found to be non-canonical for the cluster in question. Comparison with icEEG suggests that nearer regions of BOLD signal change probably relate to the epileptic network, often overlying the irritative zone or regions to which seizures propagate, while combined studies with ESI suggest that the areas of IED-related BOLD signal change may correspond to the area of spike onset or propagation (Vulliemoz, Thornton et al. 2009). This is not surprising given that in cognitive studies, both block and event related designs do not reveal single areas of BOLD signal change, but rather a network of activated brain regions about which inferences about the structure and in particular, function of cognitive networks can be drawn (Akhtari, Salamon et al. 2006, Logothetis 2008). Studies investigating the functional connectivity of regions of IED-related BOLD signal change suggest that there is altered connectivity in a variety of epilepsy syndromes both within the epileptic network and also other regions of the brain (Gholipour, Moeller et al. 2010, Moeller, Maneshi et al. 2011, Negishi, Martuzzi et al. 2011) which will be discussed in further detail below.

2.14.1 Functional Specialization and Functional Integration

The general principles underlying the study of connectivity within cerebral networks require the introduction of these concepts which are common to both physiological and pathological networks.

Historically, experimenters interpreted lesional studies as showing that sub-regions of cerebral cortex were responsible for discrete functions (for example Wernicke and
Broca who demonstrated distinct impairments in patients with focal brain lesions). Following this, in the late 19th century, however, electrical stimulation experiments and further lesional studies provided support for the theory that cerebral activity is more complicated and dependent on the interaction of different brain regions in concert (functional integration). The same principle applies to epileptic networks, where it is known that different cortical and sub-cortical regions interact, but the dynamics of these networks is not always understood.

Inferences regarding the relationship between these various regions of neuronal activity measured using various different modalities can made using measures of connectivity between regions and rely on demonstrating both correlation and causality between signals generated from them. These measures may be of ‘functional connectivity’, which simply refers to regions in which correlated pairs of signals are recorded or ‘effective connectivity’ which infers causality between brain regions.

2.14.2 Functional Connectivity (FC):

This is defined as statistical dependency or correlation between remote neurophysiological events, (which in fMRI, are reflected by regions of BOLD signal change), but in EEG or MEG would be represented by regions at which a spike arises. The relationship between two signals or nodes in a neuronal network, x and y can be described by a correlation coefficient.

Functional connectivity does not, however, allow inference about causal relationships between different nodes in a given network, meaning one can only infer that the two (or more) brain regions or neurophysiological events are correlated, but it is not possible to
discern whether x influences y, y influences x, both influence each other, or where in the network an external factor has its influence.

2.14.3 Applications of functional connectivity analysis to understanding epileptic networks

The development of sophisticated methods of analysing connectivity in epilepsy has proved invaluable, both in understanding the interaction between regions involved in the generation of seizures, and also in the development and progression of the condition. There are numerous studies which investigate connectivity within and beyond those brain networks involved in cognition which are reviewed elsewhere (Richardson 2010); recent developments relating to the understanding of the epileptic network are highlighted below.

In temporal lobe epilepsy several studies have shown abnormal connectivity in those networks concerned with language and memory function as well as the epileptic network itself; and recently it has been demonstrated that there is a disruption in interhemispheric (specifically interhippocampal) connectivity at the onset of seizures followed by increasing connectivity over time (up to 10 years following the development of epilepsy) (Morgan, Rogers et al. 2011), suggesting that fMRI connectivity can provide valuable information regarding the natural history of TLE. Moreover the same study used Granger causality to demonstrate that the contralateral hippocampus has increasing influence over the ipsilateral hippocampus as the disease developed, providing some explanation for the observation that there is a redistribution of language lateralisation in patients with dominant temporal lobe epilepsy. Another study in resting state fMRI, demonstrated a dichotomy between connectivity measured with fMRI and that measured with EEG when considering the influence of epileptic over non-epileptic
networks within subjects, raising some important questions regarding neurovascular coupling in these patients, but nevertheless demonstrating that there is altered connectivity both within and beyond epileptic networks in the brain of patients with epilepsy. Similar observations of altered connectivity have been observed in other epilepsy syndromes such as JME, in which increased functional connectivity has been reported (Vollmar, O'Muircheartaigh et al. 2011).

A further exciting potential application of functional connectivity analysis is that of measuring the likelihood of good outcome following surgery, following the observation that increased connectivity is seen over time in both TLE and other types of epilepsy (noting that increased duration of epilepsy is an independent predictor of poor outcome). One group compared connectivity measures in patients prior to undergoing surgery for different types of epilepsy using IED-related BOLD signal clusters, concordant with the resection zone as seed points. Laterality indices were calculated and the study noted that patients with less lateralised networks as measured by these indices were less likely to be seizure free than those in whom the epileptic network was more lateralised (Negishi, Martuzzi et al. 2011).

2.14.4 Measures of Causality

The observations of these studies are interesting—however it is essential in understanding the neurobiology of these epileptic networks, as with any neural network, to be able to identify forward and backward connectivity and also to be able to distinguish where the neural drivers of such networks act as well as the fact that such networks exist. In focal epilepsy, it can be considered that regions of epileptogenic cortex give rise to seizure and therefore epileptic activity arising from these foci drives
the epileptic network in a similar way to an auditory stimulus driving a network of brain regions involved in auditory networks.

To address this problem, measures of causality are used; there are various types which have evolved including Granger Causality, psychophysiological interactions and most recently dynamic causal modelling (DCM).

2.14.5 Granger Causality

Charles Granger proposed one method of demonstrating one signals influence of another based on the assumption when two signals have a temporal relationship, the one which occurs first must influence the second. Therefore, for two timecourses, $x$ and $y$, $x$ can be said to influence $y$ if $y$ can be predicted from $x$. This process is limited by the fact that if another factor (e.g. $z$) exists within a network, a coincidental causal relationship may be demonstrated between $x$ and $y$ where in fact, one does not exist. The use of Granger causality has been demonstrated in fMRI data, but is subject to the restriction in that it relies on a temporal lag between the two regions sampled and is therefore only valid for low frequency signals, rendering it less useful for the high frequency activity observed in icEEG data (David, Guillemain et al. 2008, Lemieux, Daunizeau et al. 2011).

2.14.6 Dynamic Causal Modelling

Dynamic causal modelling (DCM) is a method first developed for use in fMRI research to evaluate causal relationships between regions of the brain involved in a particular neuronal network and is a measure of effective connectivity or the ‘influence of one brain region over another’ in a neuronal network (Friston, Harrison et al. 2003). It has addressed the limitations of other measures of causality, by including information about
intrinsic ‘hidden’ neuronal states and a model of the interaction between neuronal and haemodynamic signals, such that inferences about the relationship between nodes in the neuronal network (of the order of micro or milli seconds) can be made from statistical parametric maps of fMRI (of the order of seconds). Parameters describing the both neuronal state and those which determine the forward model of BOLD signal generation are estimated from the data within a Bayesian framework for each brain area included in the model. Hence, crucially, the possibility for differing haemodynamic responses (e.g. latency between regions) is included within the DCM. The technique relies on the specification of ‘priors’ based on knowledge of the anatomical networks involved in the process under study and plausible physiological hypotheses about the behaviour of these networks. For fMRI data, Bayesian inference can then be used to determine whether the data is best explained by variations in the haemodynamic response or instead by changes in the underlying neural system. A modified approach has been developed for electrophysiological (MEG and EEG) data (Daunizeau, David et al. 2009)

While DCM has now been used to study cognitive networks where the underlying anatomy is well understood and hypotheses regarding these networks can be tested at the group level in healthy controls, its use in pathological conditions is less common. Studies in patients with Parkinsons Disease and psychosis (Rowe, Hughes et al. 2010) (Benetti, Mechelli et al. 2009) however, suggest that that useful inferences can be made regarding pathological brain networks. The value of studying effective connectivity in disease is highlighted by increasing evidence that the integrity of neuronal networks relates both to cognitive function and the clinical impact of neuronal disorders.
The use of DCM in epilepsy is intrinsically attractive as offers the possibility of studying epileptic networks using a non-invasive method, which has previously been difficult to achieve. In addition to this, it exploits the benefit of fMRI, in that whole brain coverage is achieved, which is impossible with intracranial EEG. Two studies have used the approach thus far, both addressing the issue of where epileptiform activity acts within cortico-thalamic networks in generalised spike and wave discharges (GSW), which has long been the subject of much debate (Avoli and Gloor 1982).

The first of these was a methodological validation, comparing fMRI DCM with measures of intracranial EEG connectivity in a rat model of absence epilepsy (David, Guillemain et al. 2008). In this study, the intracranial data consistently demonstrated that the discharges are driven by cortical input. General linear model base analysis of the fMRI data demonstrated GSW associated BOLD signal change in frontal cortex and the thalamus. DCM was consistently showed that the driving influence of the spike on the network was active at the cortex rather than the thalamus, in agreement with the intracranial data. The authors also demonstrated that if Granger Causality (which does not include a model for neurovascular coupling) was used, the results were not reproducible. This is important as it illustrates the problem with using a model based on lag correlation to infer relationships between neurophysiological events (of the order of milliseconds) using fMRI (of the order of seconds).

More recently, DCM has been used in humans, to attempt to demonstrate the same findings, although the group was more heterogeneous, including patients with GSW in the context of other epilepsy syndromes (Vaudano, Laufs et al. 2009). This study attempted to model the interactions between frontal cortex, thalamus and the default mode network (represened anatomically by the precuneus) and suggested that the
precuneus might have a 'gating' effect, such that the generation of GSW may be dependent on activity within this region.

A single case report has been carried out in a patient with focal epilepsy in which IED-related fMRI DCM was used to interrogate directionality between two regions in the epileptic network, with the result suggesting that it may be possible to infer a causal relationship between regions in the network (Hamandi, Powell et al. 2008).

2.14.7 Other measures of causality in epilepsy

Prior to the development of DCM, and given some of the concerns regarding the validity of its neuronal models in epilepsy, other methods of assessing connectivity have been used, particularly in icEEG, in which the methods are more established.

In addition to general measures of synchrony, applied to both interictal and ictal data sophisticated analysis of interictal activity has been developed by relaxing assumptions of linearity between pairs of signals in icEEG (Wendling, Bartolomei et al. 2001, Bourien, Bartolomei et al. 2005). Further discussion of the measures of connectivity and causality applied to epileptic networks can be found in chapter 8 and authoritative reviews have also been recently published (Wendling, Chauvel et al. 2010, Lemieux, Daunizeau et al. 2011).

2.14.8 Generalised Epilepsies

Altered connectivity has been observed in childhood absence epilepsy, JME and animal models of generalised epilepsies. Groups have demonstrated decreased connectivity in the resting state within the default mode network as well as hyper-connectivity between the various networks in Juvenile myoclonic epilepsy, which the
authors suggested might explain myoclonus in relation to cognitive tasks (Vollmar, O'Muircheartaigh et al. 2011).

2.14.9 Summary: connectivity

Despite these observational studies, the use of measures of causality, in particular DCM, remains controversial in epilepsy owing, at least in part, to the assumption of normal neuronal coupling. The work presented in chapter 8 aims to validate the method, experimentally by comparison of results of fMRI DCM with intracranial EEG in human subjects.
3 NEW EXPERIMENTS: COMMON METHODOLOGY

The methods for recruitment, scanning and pre-processing of the EEG data described in the rest of this work are common to all experiments I conducted are described below in order to avoid repetition. The details specific to individual experiments are described at the beginning of the relevant section of Chapter 4.

3.1.1 Recruitment

102 patients with refractory focal epilepsy undergoing pre-surgical evaluation underwent EEG-fMRI between December 2005 and May 2009. Patients were selected during pre-surgical evaluation, following the decision to undertake intracranial EEG recording, either to more accurately localise the seizure onset zone or to differentiate the seizure onset zone from eloquent cortex.

Patients were recruited from 4 centres, the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, Kings College Hospital, Denmark Hill, London, UK, North Bristol Hospitals NHS Trust, Frenchay, Bristol, UK and Hopital de la Timone, Marseille, France. Written consent for participation in the experiments and information retrieval from medical records was obtained for all patients (see Appendix A). The experiments were all approved by the relevant local and National Ethics and Research and Development Committees at all centres.

3.1.2 Exclusions

All patients who were selected for icEEG recording at each centre were considered for EEG-fMRI recording and eligible patients were contacted by telephone and/or letter. Patients were excluded if they had contraindications to MRI (vagus nerve stimulator (VNS) or other implanted device). Patients who did not wish to undergo either EEG-
fMRI scanning or icEEG were excluded at this stage. Patients were all provided with written ‘Patient information sheets’ prior to attending for the procedure and were given the opportunity to obtain further information by telephone or in person prior to scanning. Written consent was obtained from all patient prior to participating in the study (Copies of patient information sheets and Consent forms are provided in appendix A for reference).

In total 140 patients were identified and contacted of whom 39 did not undergo EEG-fMRI. Reasons included presence of VNS (n=6, all from Kings College Hospital), cardiac pacemaker (n=2, KCH and NHNN) and declining to participate for other reasons (n=20, from all four centres, usually owing to the fact the patients felt it was too far for them to travel). Two patients attended, but did not undergo the study, one owing to claustrophobia and the second because the patient had a recent history of injury resulting in a metal foreign body in the eye.

3.1.3 Clinical course

Patients underwent electro-clinical assessment including video EEG, clinical examination and structural MRI at 3T including T1-weighted volumetric scan, T2, T2 FLAIR, and FSE according to the Epilepsy Society protocol. Some patients also underwent Magnetoencephalography (MEG), ictal single photon emission tomography (SPECT), positron emission tomography (PET) and/or WADA testing depending on their local centre’s clinical protocol. A clinical history and neurological examination was undertaken at the time of the experiment, and clinical details, scalp video-EEG and other relevant data was retrieved from each patient’s medical record.

Any decision regarding electro-clinical localisation, invasive recording and subsequent resection was made by each patient’s own clinical team and undertaken with curative
intent. Results and data from intracranial EEG recordings including imaging data were retrieved from the patients record where relevant. The extent of resection, histopathological diagnosis and International League Against Epilepsy (ILAE) outcome (Wieser, Blume et al. 2001) were recorded at 6 months, 1 year and at one year intervals following resection.

3.1.4 EEG-fMRI Acquisition

Scalp EEG-fMRI sessions all took place at the Epilepsy Society MRI Unit, Chalfont St Peter, UK using GE MR Scanners. Studies at 1.5 T were carried out on a GE Horizon Echospeed scanner while those at 3T were carried out on a GE 3T short bore Excite scanner. EEG was recorded using a MRI compatible cap with 32 or 64 electrodes according to the international 10-20 system (Brain Products, Munich, Germany). An initial baseline EEG recording was made for 5-20 minutes prior outside the scanner with eyes closed in a dark room. All patients then underwent EEG-fMRI for 35 minutes at 1.5T (n=3 patients in the post-operative series only) or 2-3 x 20 minute sessions at 3T (n=99) depending on patient tolerance. Patients lay still in the scanner with their eyes closed and with no instruction regarding vigilance. EEG was recorded continuously during fMRI using MR-compatible systems (Brain Products, Munich, Germany) along with a scanner synchronisation signal and ECG. Sets of 404 T2*-weighted single-shot gradient-echo echo-planar images (EPI; TE/TR 30/3000 msec at 3T; TE/TR 0.5/3000 msec at 1.5T), flip angle 90°: 43 (at 3T) or 21 (at 1.5T), interleaved slices (thickness: 3mm at 3T; 5mm at 1.5T), FOV 24x24cm², 64²) were acquired continuously on GE MR scanners (GE Medical Systems, Milwaukee). Following this, patients underwent a 5 minute fingertap motor fMRI study with a block design (30
seconds, tap right hand, 30 seconds, tap left hand, 30 seconds rest repeated in sequence for 300 seconds) for validation of the experiment.

3.1.5 EEG pre-processing

Offline MRI artefact and pulse related artefact were removed from the EEG trace recorded during scanning using a template subtraction method described elsewhere (Allen, Polizzi et al. 1998, Allen, Josephs et al. 2000) implemented in a commercial EEG processing package (Brain Analyzer, Brain Products, Munich, Germany). ECG complexes were marked and a second template subtraction method used to subtract pulse related artefact from the EEG. All EEG recordings were then inspected and IEDs and seizures coded by at least two observers (RT, HL, SC, SV, UC).

Factual descriptions of all events and the background EEG were produced by an observer for each case. Sleep stages were noted for comparison with other data. Events were verified as typical for each patient by comparison with the patients long-term scalp video EEG monitoring carried out during pre-surgical evaluation.

3.1.6 fMRI pre-processing

The fMRI time-series were realigned using a rigid body transformation and spatially smoothed with a cubic Gaussian Kernel of 8 mm full width at half maximum in SPM5 (www.fil.ion.ucl.ac.uk) for standard General linear model analyses, while a second pre-processing was carried out in SPM8 for patients included in the dynamic causal modelling group as there are significant differences in the DCM methodology between the two versions.
3.1.7 General Linear Model Analysis of IED-related BOLD signal change

3.1.7.1 Specification and Estimation of the model

Separate sets of regressors were formed for each type of IED (allowing identification of specific BOLD effects) using Matlab version 6.5 or 7.1 to derive a timecourse of IEDs for each EEG. Discharges were represented as zero-duration events (unit impulse, or ‘delta’, functions) which were convolved with the canonical haemodynamic response function its temporal and dispersion derivatives, resulting in three regressors for each event type (Friston, Fletcher et al. 1998). Motion-related effects were included in the GLM as 24 regressors representing 6 scan realignment parameters and a Volterra expansion of these (Friston, Frith et al. 1995), and Heaviside step functions for large motion effects with the exception of patients in whom seizures were recorded (see chapter 7) (Lemieux, Salek-Haddadi et al. 2007). Additional regressors were included for pulse-related signal changes (Liston, Lund et al. 2006). A typical GLM is shown in Figure 3-1.
In those patients who had seizures during the recording, the modelling approach is described separately in the relevant chapter. Models were estimated in SPM5 using the classical model estimation. A second GLM analysis was carried out in SPM8 for the DCM group (see chapter 8.3).

3.1.7.2 Contrast specification

F-contrasts were used across three regressors corresponding to each event type with a threshold of $p<0.05$ corrected for multiple comparisons (family-wise error) considered significant. A T-contrast ($p<0.001$ uncorrected for multiple comparison) assessed whether the haemodynamic response function was positive or negative. BOLD responses were considered positive when a positive HRF was plotted for a given
cluster. A less stringent significance threshold was used to explore the data (p<0.001, uncorrected for multiple comparisons).

3.1.8 Comparison with Post-operative Imaging

EPI data were co-registered to the pre-operative T1-weighted images to create activation map overlays. Clusters of significant BOLD change were labelled anatomically on high resolution EPI images and co-registered with pre-operative structural T1 images.

3.1.9 Comparison of fMRI patterns with Intracranial EEG: Interictal Data

Comparison of whole brain patterns of activation derived from EEG-fMRI experiments and the intracranial EEG in particular is difficult as it relies on summarising a number of BOLD signal clusters on a whole brain map and comparison with a single or multiple seizure onset zone(s). This comparison is traditionally expressed as a degree of ‘concordance’. The classification of concordance used in this thesis is based on that used by our group and others, but evolved during the course of the work following evidence which suggests that the ‘global maximum’, traditionally given a place of particular significance in our classification scheme, is not always associated with the region of spike onset, but may reflect regions of spike propagation (Vulliemoz, Lemieux et al. 2010). Thus for the earlier work (initial comparisons of IED-related BOLD signal change with resection data), the original classification scheme was used and in subsequent work for formal comparison with intracranial data a modified classification scheme was employed.

1. Original classification used in the initial post-operative outcome study:
• **Concordant (C):** The entire BOLD map was concordant with the site of seizure onset identified either on icEEG or the epileptogenic zone (EZ) following resection.

• **Concordant plus (C+):** The cluster containing the global maximum statistical maximum was concordant but additional, discordant clusters were revealed.

• **Discordant (D):** All clusters were remote from the seizure onset zone.

2. Modified classification scheme (used for comparison of IED-related BOLD signal change with intracranial EEG in chapters 6 - 8).

• **Concordant (C),** when all significant BOLD clusters were concordant with the site of seizure onset identified on intracranial EEG, defined when the area of maximal signal change was in the same lobe and within 2cm of the intracranial EEG electrode marking seizure onset.

• **Concordant+ (C+)** when one the most significant BOLD signal cluster was concordant but additional, remote statistically significant clusters were also revealed within or bordering the same lobe,

• **Discordant+ (D+)** when significant cluster(s) were concordant with the seizure onset zone, but additional widespread clusters were observed outside of the same lobe

• **Discordant (D),** when no cluster was concordant

• **NULL,** when no significant activation was revealed
The figure of 2cm was used as a cut off between intracranial electrodes and fMRI clusters provided they were in the same anatomical location to allow for the potential coregistration inaccuracies arising from cortical displacement during implantation of depth electrodes, following the observation that 2cm shift, typically needs to be accounted for when comparing icEEG with pre-operative imaging data (Nimsky, Ganslandt et al. 2000).

### 3.1.10 Ictal Group

Methodology is described in chapter 7 for this group.
4 RESULTS:

The pre-surgical EEG-fMRI scans were done prospectively over a period of three years, during which my approaches to data analysis evolved. The presentation of the results reflects this starting with the initial pilot study and pathological subgroups and moving on to the investigation of more complex networks and ictal data as this makes more scientific sense rather than a strict chronological progression. The final chapter summarises the data acquired over the course of the project. The timeline below illustrates how the experiments and results occurred chronologically.

4.1 Details of patients

101 (54 male) patients with focal epilepsy were recruited and scanned over 4 years for the purpose of this study. All were awaiting icEEG implantation and patients were recruited to the study following the decision to implant.

Of 101 patients, 2 were excluded from any further analysis. One moved abroad and declined to take part in any further evaluation and one patient died shortly after the EEG-fMRI scanning session (sudden unexpected death in epilepsy (SUDEP)). The final patient’s episodes were found to be non-epileptic following further non-invasive investigation.

Of the remaining 99 patients, 46 had IEDs during scanning and 37 had IED-related BOLD signal change (summarized in chapter 10). 9 patients had seizures (of whom 3 had no IEDS during scanning).
There is some overlap between the patients reported in chapters 5 and 6 as the two experiments addressed different questions. Similarly there is some overlap between the patients included in chapters 5, 8 and 10.
Table 4.1 Timeline of experimental work related to developments in methodology

<table>
<thead>
<tr>
<th>Year</th>
<th>Developments in methods</th>
<th>Progress of patients and experimental work</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>3T MRI Scanner in place at the Epilepsy Centre</td>
<td>Recruitment and scanning underway at 3T</td>
</tr>
<tr>
<td>2007</td>
<td>First report of the use of ICA applied to EEG-fMRI data (Rodionov, De Martino et al. 2007)</td>
<td>Continued data collection and initial ‘pilot group’ of patients with IEDs identified icEEG acquisition continues.</td>
</tr>
<tr>
<td>2008</td>
<td>Satisfactory method for fusion of T1 weighted MRI and CT allowing coregistration between EPI and implanted images Planning in place for first icEEG-fMRI scanning in vivo</td>
<td>Pilot group of first 10 patients with IEDs reach one year follow up (Chapter 5) Data collection continues icEEG analysis begins</td>
</tr>
<tr>
<td>2009</td>
<td>SPM8 launched with more sophisticated dynamic causal modelling software</td>
<td>Pilot group submitted for publication 9 patients with seizures identified with adequate follow up and icEEG. Development of modified GLM and ICA methods applied in this group (Chapter 7) Ictal group submitted for publication DCM analysis begun. First icEEG-fMRI cases scanned</td>
</tr>
<tr>
<td>2010</td>
<td>Completion of EEG-fMRI data acquisition early 2010. Identification of largest pathological sub-group in whom adequate follow up is available (focal cortical dysplasia) and analysed (Chapter 6) Ictal icEEG-fMRI recorded Initial DCM Analysis completed</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>fMRI-DCM methodology evolves to include Bayesian Model Comparison in epilepsy data (Murta, Leal et al. 2012)</td>
<td>EEG-fMRI in FCD group reach one year follow up. Submitted for publication. Ictal icEEG-fMRI data initial analysis complete (Chapter 9).</td>
</tr>
<tr>
<td>2013</td>
<td>Entire group reach 3 year follow up period (Chapter 10) DCM analysis complete (chapter 8)</td>
<td></td>
</tr>
</tbody>
</table>
5 EXPERIMENT 1: PILOT STUDY COMPARING IED RELATED BOLD SIGNAL CHANGE WITH POST-OPERATIVE OUTCOME

5.1 Summary

Aim:

The initial study was designed to provide preliminary information about the clinical utility of EEG-fMRI by comparing the results of IED-related BOLD signal change with post-operative structural MRI. As has been discussed above, in patients with focal epilepsy, interictal epileptiform discharge (IED) correlated blood oxygen dependent level (BOLD) signal changes have been observed in approximately 50% of patients in whom IEDs are recorded and IED related BOLD signal change was concordant with seizure onset (defined by non-invasive data) in 70% of these. Assessment of clinical validity requires comparison with postoperative outcome and resected areas. In the experiment presented here, IED correlated fMRI signal changes were related to the resection area and clinical outcome a pilot group of 10 patients identified at the mid-point of the study. My hypothesis was that if the area of resection included those regions in which IED-related BOLD signal change was observed, post-operative outcome would be favourable compared with those in whom large areas of BOLD signal change lay outside the resected region.

Methods:

76/101 patients who underwent EEG-fMRI according to the above protocol (see section 3.1.1) had been studied at the time of the first experiment. Patients who had IED-related BOLD signal change, subsequently had respective surgery and reached a
1 year post-operative follow up period at the time of analysis, were selected. The locations of IED related BOLD signal change were compared with post-operative structural MRI and post-operative outcome at one year in each patient.

Results:

21/76 patients had activations with epileptic activity on EEG-fMRI and 10 underwent surgical resection with adequate follow up. Seven of 10 patients were seizure free following surgery and the area of maximal BOLD signal change was concordant with resection in six of seven patients. In the remaining three patients, with reduced seizure frequency post-surgically, areas of significant IED correlated BOLD signal change lay outside the resection.

Conclusion:

These results show the potential value of EEG-fMRI in presurgical evaluation and led to further experiments exploring the relationship between IED-related BOLD signal change and intracranial EEG findings and a more extensive follow up study.

5.2 Introduction:

In refractory focal epilepsy, surgical resection has the best chance of a good outcome if seizure onset is identified and remote from eloquent cortex (Rosenow and Luders 2001).

As discussed above, high quality structural MRI has increased the identification of underlying pathology in epilepsy but successful resective surgery is increasingly possible in the absence of MRI abnormalities, when icEEG is often required
(McGonigal, Bartolomei et al. 2007) although the epileptogenic zone may extend beyond the margin of abnormal tissue where pathology is seen. Intracranial EEG recording requires careful patient selection and only 70–90% of such patients will subsequently be offered surgical resection (Cossu, Cardinale et al. 2005).

Novel non-invasive techniques including radionucleide imaging as well as neurophysiological approaches (high density EEG and MEG) have shown concordance with icEEG and postoperative outcome (Knowlton, Elgavish et al. 2008) (Knowlton, Elgavish et al. 2006, Knowlton, Elgavish et al. 2008), but are limited by poor temporal and spatial resolution respectively (see section 2.8 -2.10).

To date, clinical validation of EEG-fMRI has consisted of studies comparing IED correlated BOLD signal change with invasive and non-invasive methods of localising the seizure onset zone, (Krakow, Woermann et al. 1999, Lazeyras, Blanke et al. 2000, Krakow, Lemieux et al. 2001, Al-Asmi, Benar et al. 2003, Salek-Haddadi, Diehl et al. 2006, Jacobs, Kobayashi et al. 2007) in patients with focal epilepsy, but these studies were not limited to patients undergoing pre-surgical evaluation and therefore did not relate specifically to outcome.

Comparison of novel localisation techniques in focal epilepsy with intracranial EEG, the current gold standard, is considered the best method for validation but the approach has drawbacks as discussed in section 2.11.3. Nevertheless, it remains one of the best methods of identifying the likely irritative and epileptogenic zones before resection. In order to establish clinical utility, however post-operative outcome is also extremely important as the EZ cannot be identified definitively until after resection.

In EEG-fMRI research, concordance of activations with the irritative zone recorded
during invasive monitoring had been reported in small groups at the time of this experiment, an important step in establishing the technique's clinical utility and two studies had specifically addressed its value in pre-surgical evaluation in small groups of patients discussed further in section 2.13.4.4 (Al-Asmi, Benar et al. 2003) (Zijlmans, Huiskamp et al. 2007, Moeller, Tyvaert et al. 2009).

Much of the work presented in this thesis is aimed at comparing the results of EEG-fMRI with intracranial EEG; however I also undertook an initial study, comparing patterns of haemodynamic change with post-operative outcome which forms the first experiment. I compared EEG-fMRI results in a group of patients undergoing surgery with postoperative outcome, assessing whether resection of a region exhibiting IED correlated BOLD activation was associated with postoperative seizure freedom.

5.3 Methods

5.3.1 Patients

76/101 consecutive patients described in section 3.1 with refractory focal epilepsy undergoing presurgical evaluation with IEDs recorded during video telemetry underwent EEG-fMRI between December 2005 and May 2008 and were followed up for at least 12 months. The EEG-fMRI results did not form any part of the surgical decision making process and were undertaken independently from other investigations without any reduction in medication.

5.3.2 Clinical course

Patients underwent electroclinical assessment as described in section 2. The decision regarding electroclinical localisation and subsequent resection was made by the clinical
team and undertaken with curative intent. Six patients underwent anterior temporal lobe resection and four underwent neocortical resection (two frontal, one parietal and one occipital).

The extent of resection, histopathological diagnosis and International League Against Epilepsy (ILAE) outcome described in section 1 (Wieser, Blume et al. 2001) were recorded 1 year postoperatively.

5.3.3 EEG-fMRI acquisition

All patients underwent EEG-fMRI for between 35 and 60 min at 1.5 or 3 T; the 3T recording details are given in section 2. Patients lay still in the scanner with their eyes closed and with no instruction regarding vigilance. EEG was recorded continuously during fMRI using MR compatible systems (Brain Products, Munich, Germany) along with a scanner synchronisation signal and ECG. Sets of 404 T2* weighted single shot gradient echo, echo planar images (EPI; TE/TR 30/3000 ms at 3 T; TE/TR 0.5/3000 ms at 1.5 T), flip angle 90° 43 (at 3T) and 21 (at 1.5T), interleaved slices (thickness: 3mm at 3 T; 5mm at 1.5 T), FOV 24×24 cm², 64²) were acquired continuously on GE MR scanners (GE Medical Systems, Milwaukee, Wisconsin, USA). Offline MRI and pulse related artefacts were removed from the EEG trace and events marked.

5.3.4 fMRI processing and analysis

The fMRI time series were realigned, spatially smoothed with a cubic Gaussian kernel of 8 mm full width at half maximum and analysed using a general linear model in SPM5 (http://www.fil.ion.ucl.ac.uk/SPM) to identify IED related BOLD changes as described in chapter 3. Three regressors were formed for each IED type as in section 3.1.7. Ictal events were represented as blocks with onset and offset corresponding to the
beginning and end of each seizure on scalp EEG.

Motion related effects were included in the general linear model as 24 regressors representing six scan realignment parameters and a Volterra expansion of these, and Heaviside step functions for large motion effects. Additional regressors were included for pulse related signal changes.

F contrasts were used across three regressors corresponding to each event type with a threshold of p<0.05 corrected for multiple comparisons (family-wise error) considered significant. A T contrast (p<0.001 uncorrected for multiple comparison) assessed whether the haemodynamic response function was positive or negative. BOLD responses were considered positive when a positive haemodynamic response function (HRF) was plotted for a given cluster. A less stringent significance threshold was used to explore the data (p<0.001, uncorrected) and the results noted when the more stringent threshold did not reveal any BOLD signal change. EPI data were coregistered to the preoperative T1 weighted images to create activation map overlays. Clusters of significant BOLD change were labelled anatomically on high resolution EPI images and coregistered with preoperative structural T1 images.

5.3.5 Postoperative imaging

Postoperative T1 weighted MRI was acquired and coregistered with the preoperative images allowing visualisation of fMRI activation maps in relation to the area of resection. Concordance was defined for the cluster of BOLD activation containing the global maximum.
5.3.6 Results

76 patients had undergone EEG-fMRI recordings at the time of this experiment. 52 (68%) subsequently underwent surgical resection. 34/52 (65%) had reached one year follow up of whom 10 (33%) had significant activation on EEG-fMRI at the time of this analysis. A further 11 had significant activation on EEG-fMRI, but did not undergo surgery owing to an extensive epileptogenic zone or overlap with motor function (n=5), intra-operative complications (n=1), patient choice (n=1) or awaiting further evaluation (n=4). In 36/52 (69%) patients who were operated and 13/24 (54%) who were not operated, no IEDs were recorded. This pilot group included 3 patients who underwent EEG-fMRI prior to the main cohort on a 1.5 T scanner and subsequently underwent surgery (patients 1-3).

Clinical data and EEG-fMRI results are summarised in Table 5.1. The median number of IEDs was 329 (range 22-635). Case reports are presented below together with representative figures from the case series.

EEG recorded in scanner:

In 8/10 patients only one event type was recorded during EEG-fMRI sessions. In the remaining two patients (cases 5 and 8, two types of IED were recorded as described below)
**Table 5.1 Electroclinical data for pilot study**

<table>
<thead>
<tr>
<th>Case</th>
<th>Scanner (Tesla)</th>
<th>Electro-clinical localisation</th>
<th>Semiology</th>
<th>Structural MRI</th>
<th>Pathology</th>
<th>ILAE outcome</th>
<th>EEG fMRI Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>L mesial TLE</td>
<td>Epigastric aura, Oroalimentary automatisms.</td>
<td>L HS</td>
<td>HS</td>
<td>1</td>
<td>L anterior temporal lobe (FWE p&lt;0.05)</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>L mesial TLE, L</td>
<td>Epigastric aura, oroalimentary automatisms, L-manual automatisms.</td>
<td>L HS</td>
<td>HS</td>
<td>1</td>
<td>Anterior portion L inferior temporal gyrus (FWE p&lt;0.05)</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>L TLE.</td>
<td>From sleep. Nauseated, hyperventilation. L-sided manual automatisms.</td>
<td>L HS</td>
<td>HS</td>
<td>1</td>
<td>L anterior temporal lobe (FWE p&lt;0.05)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>R TLE.</td>
<td>Hyperventilation, confusion. Bilateral manual automatisms.</td>
<td>R HS, previo resection</td>
<td>HS</td>
<td>1</td>
<td>R mesial temporal lobe (unc. p&lt;0.0001)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Non-lateralised TLE. Ictal iEEG: bilateral EZ</td>
<td>Behavioural arrest, fear, right hand dystonia, head turning to R.</td>
<td>L HS</td>
<td>HS</td>
<td>1 *</td>
<td>R and L lateral temporal lobes (FWE p&lt;0.05)</td>
</tr>
</tbody>
</table>

R = right, L = left, F= frontal, T = temporal, P= parietal, LE= lobe epilepsy, FCD = focal cortical dysplasia, IED = interictal epileptiform discharges, FWE = family wise error, HS = hippocampal sclerosis, EZ = epileptogenic zone, IZ = irritative zone
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Side</th>
<th>Diagnosis</th>
<th>Details</th>
<th>Location</th>
<th>Grade</th>
<th>IED</th>
<th>Ictal Details</th>
</tr>
</thead>
</table>
| 6    | 3   | R    | TLE       | Hyperventilation, loss of awareness, manual automatisms | R HS | HS | 1 | Ictal: Right mesial temporal (FWE p<0.05) 
IED: none |
| 7    | 3   | R    | posterior epilepsy | Visual hallucination, incontinence, loss of awareness | R occipital FCD | FCD | 4 | Ictal: Right medial occipital (FWE p<0.05) 
IED: none |
| 8    | 3   | L    | FLE. Ictal icEEG, EZ posterior to FCD. Widespread EZ | From sleep, unresponsive, but awake. Rapid blinking. R arm posturing. Head turning to R. | L inferior frontal gyrus FCD | FCD grade 2a | 4 | L pre-central gyrus and superior temporal gyrus |
| 9    | 3   | R    | PLE       | Sensory change left foot, clonic movements left arm and leg | R parietal FCD | FCD grade 2a | 1 | Ictal: Maximal right parietal, but widespread (FWE p<0.05) No IED |
| 10   | 3   | R    | FLE       | Speech arrest, head version to L, clonic movements L hand and foot | R frontal atrophy | Normal | 4 | IED and ictal |

R = right, L = left, F = frontal, T = temporal, P = parietal, LE = lobe epilepsy, FCD = focal cortical dysplasia, IED = interictal epileptiform discharges, FWE = family wise error, HS = hippocampal sclerosis, EZ = epileptogenic zone, IZ = irritative zone
5.3.7 Case reports

Case 1: Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis on structural MRI at 1.5 Tesla. Interictal EEG revealed left temporal spikes. EEG-fMRI showed widespread activation in the left anterior temporal lobe. Comparison with the post-operative T1 weighted MRI showed the IED-related BOLD cluster within the resection margins. The patient is seizure free (ILAE class 1) 38 months post-surgery (Figure 5-1).

![EEG-fMRI and post-operative MRI in patient 1.](image)

A: Results of IED-related BOLD signal change overlaid on high resolution EPI. IED-related activation in the left anterior temporal lobe. Crosshair lies at the statistical global maximum (SPM(T) test, \(p<0.05\) FWE corrected, \(z=6.69\). B: Plotted response for the same events at global maximum. Event (spike) related haemodynamic response +90% confidence interval (broken lines). Time=time in seconds after event. C: Same region of BOLD signal change coregistered to and overlaid on post-operative T1 weighted MRI showing resection cavity.
Case 2: Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis on structural MRI. Interictal EEG revealed left temporal spikes. EEG-fMRI showed activation in the left anterior temporal lobe. Comparison with the post-operative scan showed the IED-related BOLD activation contained within the resection. The patient is seizure free (ILAE class 1) 49 months post-surgery.

Case 3: Patient with left mesial temporal lobe epilepsy and left hippocampal sclerosis. Interictal EEG revealed left temporal spikes. EEG fMRI showed activation in the left anterior temporal lobe. Comparison with the post-operative scan showed the IED related BOLD activation contained within the resection. The patient is seizure free (ILAE class 1) 30 months post-surgery.

Case 4: Patient with right hippocampal sclerosis and previous resection for a right superior temporo-parietal cavernoma. EEG-fMRI revealed activation in the right mesial temporal lobe. Right anterior temporal lobe resection following confirmation of seizure onset on intracranial EEG was carried out. Comparison with the post-operative scan showed the IED related BOLD activation contained within the most recent resection. The patient remains seizure free. (ILAE class 1) 24 months post-surgery.

Case 5: Patient with left hippocampal sclerosis. EEG showed independent right and left temporal IEDs. EEG-fMRI revealed bilateral temporal BOLD activations. Intracranial recording demonstrated 70% of seizures originated from left mesial temporal structures with a further 30% having simultaneous bilateral onset, and left anterior temporal lobe resection was carried out. The patient has had no further complex partial seizures 18 months post-surgery, but medication was unchanged and the EEG remains extremely active over the right temporal electrodes (ILAE 1) (Figure 5-2).
Figure 5-2: EEG-fMRI and post-operative MRI in patient 5.

A: Results of IED-related BOLD signal change overlaid on high resolution EPI. IED-related activation in the left anterior temporal lobe. Crosshair lies at the statistical global maximum (SPM(T) test, p<0.05 FWE corrected, z=6.69. B: Plotted response for the same events at global maximum. Event (spike) related haemodynamic response +90% confidence interval (broken lines). Time=time in seconds after event. C: Same region of BOLD signal change coregistered to and overlaid on post-operative T1 weighted MRI showing resection cavity.
Case 6: Patient with right hippocampal sclerosis. EEG revealed right temporal sharp waves. Interictal EEG-fMRI demonstrated BOLD deactivation in the default mode network, but no activation was observed. Ictal EEG-fMRI demonstrated activation in the right anterior temporal lobe, with deactivation in the right posterior temporal lobe and contralateral hemisphere. Right anterior temporal lobe resection was carried out and the area of maximal activation lay within resection margins. The patient is seizure free (ILAE class 1) 14 months post-surgery.

Case 7: Patient with right occipital-parietal cortical dysplasia. Electroclinical localisation suggested right occipital onset. During EEG-fMRI two seizures were recorded with widespread posterior slowing on EEG. Maximal BOLD activation was recorded in the right medial occipital lobe associated with the earliest detectable change on EEG. Intracranial recording revealed seizure onset predominantly in the right lateral occipital lobe, but the irritative zone also involved right mesial and left sided contacts. A wedge resection was carried out in the right occipital and parietal lobes and the patient has a reduced number of seizures 12 months following surgery (ILAE class 4).

Case 8: Patient with FCD in the left middle frontal gyrus on MRI. EEG revealed left frontal spikes and rapid discharges. The lesion was not concordant with the most significant IED correlated left frontal BOLD activation, but an activation at a lower level of significance (p<0.001 uncorrected for multiple comparisons) in the left anterior frontal lobe was observed correlated with rapid discharges on the EEG. Intracranial recording demonstrated an extensive irritative zone with seizure onset anterior to the lesion concordant with the less significant BOLD activation, and independent spikes in inferior frontal lobe and superior temporal depth electrodes. Left frontal lobe resection was carried out with seizure frequency halved (ILAE class 4) 27 months post-surgery.
Case 9: Patient with right post-central gyrus FCD on 3T-MRI. Electro-clinical localisation suggested right parietal seizure onset. During EEG-fMRI there were no IEDs, but two electrographic seizures were recorded with build up of fast activity at Fz-F4 followed by right sided slowing. Fast activity was correlated with intense, widespread BOLD signal change bilaterally in the paramedian frontal and parietal lobes, which was marked on the right side. Intracranial EEG confirmed seizure onset in the right medial post-central gyrus. The patient is seizure free following resection of FCD (ILAE class 1) 12 months post-surgery.
Case 10: Patient with right frontal atrophy (Figure 5-3). Electroclinical localisation suggested right pre-frontal seizure onset. During EEG-fMRI, bifrontal spike wave discharges were recorded most marked in F4. Electrographic seizures were recorded with similar EEG appearance. Maximal BOLD activation in the right mesial pre-motor cortex with further clusters in the right supplementary motor area and right orbitofrontal cortex was associated with both ictal and interictal activity. Limited right frontal resection was carried out guided by intracranial EEG, and the region of activation extended beyond resection margins. Seizure frequency was unchanged at 12 months (ILAE class 4).

Figure 5-3 EEG-fMRI results and post-operative MRI in patient 10.

A. IED-related BOLD signal change overlaid on EPI. IED-related activation in the right mesial frontal lobe. Crosshair lies at the statistical global maximum (SPM(T) test, p<0.05 FWE corrected, z = 7.6). B. Plotted response for the same events at global maximum. Event (spike) related haemodynamic response +90% confidence interval (broken lines). Time=time in seconds after event.. (C) Postoperative resection seen on T1 weighted MRI.
5.4 Discussion

This series of patients with refractory focal epilepsy demonstrates good correspondence between the localisation of IED-related BOLD changes, the area of resection and seizure outcome, with useful information gleaned in 10/34 patients in whom resections were carried out and the requisite follow up period reached. In six of the seven cases that are seizure free post-operatively, the area of resection included the locus of maximum BOLD signal increase. No IED was captured during EEG-fMRI in case 6 but one cluster of ictal-correlated BOLD signal increase lay within the resection margin. In the remaining three patients who continued to have seizures after surgery the areas of maximal BOLD activation did not overlap with the resected area. Although the clinical outcomes in these patients are expected given their diagnoses, these results support the contention that IED and ictal EEG-fMRI BOLD signal change are linked to seizure onset zone in focal epilepsy. The EEG-fMRI data did not contribute to the surgical decision giving an unbiased evaluation of a potential role of the technique and following these observations, more extensive systematic comparison of IED-related BOLD signal change, icEEG and post-operative outcome were carried out (see following sections).

5.4.1 Methodological Considerations

5.4.1.1 EEG fMRI yield and confounding factors

EEG-fMRI relies on the recording of events during the scanning period, a problem shared with both MEG and standard EEG. Events were captured in 21 of the 76 patients in this group (10/34 who underwent resection), which appears low, but previous studies of EEG-fMRI often exhibit a selection bias, considering only patients with a very active resting EEG in contrast to this study. Low yield has been a recurrent
problem in EEG-fMRI experiments and there have been recent attempts to improve this with the use of novel imaging techniques such as magnetic resonance encephalography (a MRI sequence allowing fMRI acquisition with temporal resolution of 100 msecs) combined with EEG (EEG-MREG), which the authors claim has much better sensitivity compared with conventional EEG-fMRI using EPI sequences (Jacobs 2012) or modified approaches to analysis of the intra-MRI EEG, discussed in further detail later in this thesis (Grouiller, Thornton et al. 2011).

The approach to fMRI data modelling is designed to ensure that regional BOLD changes explained by confounding factors are not considered as effects of interest, by incorporating these features in the model. I used a stringent threshold of p<0.05 FWE corrected for multiple comparisons, but in one case have reported the uncorrected, but statistically significant result as this is confirmed on icEEG.

Rigid techniques were employed to correct for physiological noise by not only including realignment parameters in the model, but also by the use of a scan nulling technique when motion exceeded 1mm (Lemieux, Salek-Haddadi et al. 2007). While the statistical tools used to produce maps of activity are designed to control for rates of false positive findings, lack of significant BOLD activation essentially represents low signal-to-noise ratio (particularly owing to high noise reflecting variance in the baseline), which may be scanner-related or physiological. While conservative measures to correct for physiological noise improve the specificity of the model, they also reduce sensitivity if an event of interest correlates with motion (this is particularly applicable to seizures).

It seems clear that BOLD increases generally reflect increases in neuronal activity, but in the case of epileptic activity recorded on EEG the relationship is not so clear-cut. Previous reports suggest seizures and IEDs associated with a positive BOLD response
(Kobayashi, Bagshaw et al. 2006) (Salek-Haddadi, Diehl et al. 2006), however BOLD decreases have also been observed and seizure related BOLD signal change was explored further in this experiment (see section 3.3). Importantly, lack of activation does not allow any firm inferences to be made on the level of brain activity and in particular lack of regional epileptic activity in this context.

5.4.1.2 Limits of an interictal study

Caution is required in extrapolating the results of any interictal investigation to make inferences about the epileptogenic zone, although the development of an interictal method that may contribute to identification of the epileptogenic zone has advantages. It is clear that EEG-fMRI does not image the epileptogenic zone even in the context of ictal recordings, but rather that these results are concordant with seizure onset in straightforward cases and may offer hypotheses for further evaluation in complex cases.

5.4.1.3 Comparison of EPI and T1 weighted imaging

Coregistration of T1 images and EPI for the localisation of BOLD signal change is problematic particularly when complicated by changes in brain structure. I addressed this by comparing individualised SPMs of BOLD signal change with each subject’s postoperative T1 volume scan, ensuring accurate anatomical localisation of the area of BOLD signal change. Spatial smoothing limits the resolution of EPI, but visual comparison was adequate to compare activations with the resected region. This was of particular relevance when looking at patients with temporal lobe epilepsy, given the signal drop out within this region and is discussed further when considering the whole cohort in section 10.
5.4.2 Clinical Significance

Previous studies in focal epilepsy demonstrate regions of IED-related BOLD signal change, often concordant with the seizure onset zone determined by electro-clinical localisation both in temporal and extra-temporal lobe epilepsy and our data support these findings (Krakow, Lemieux et al. 2001, Al-Asmi, Benar et al. 2003, Salek-Haddadi, Diehl et al. 2006).

Validation of the technique’s clinical use must now depend on demonstrating added value and can be achieved by comparing the EEG-fMRI findings with those of intracranial EEG. However, successful demonstration of a new localisation technique’s capability to predict post-surgical outcome remains the gold standard against which all localisation methods are judged. In this series I observed that resections which completely removed the region in which IED correlated BOLD signal change were generally associated with seizure freedom, while the finding that areas of significant BOLD activation lying outside of the resection was predictive of poorer outcome in this unbiased sample. It can be argued that the outcomes are unsurprising given the diagnoses, especially in patients with hippocampal sclerosis, but this is a test that any new technique must pass.

In case 5, bilateral activations were observed in relation to runs of left temporal IED, while electroclinical evaluation suggested bilateral seizure foci (clinical seizure arising from the left temporal lobe and electrographic seizures recorded at the right temporal lobe contacts on icEEG). Despite the lack of seizures post surgically, routine scalp EEG remained very active following resection with frequent runs of IEDs, an independent predictor of poor outcome (Godoy, Luders et al. 1992, Knowlton, Elgavish et al. 2008). This lends support to the theory that multiple EEG-fMRI activations may be predictive of poor outcome in surgery, which we have explored further in a
pathology specific comparison of icEEG and IED-related BOLD signal change in patients with FCD presented in Chapter 6. Cases 7, 8 and 10, in which the most significant activations lay outside the region of resection and the epileptogenic and irritative zones were confirmed to be extensive on intracranial recording, lend further support to this hypothesis.

In cases 6 and 9 interpretation is more difficult as ictal activity was recorded during EEG-fMRI. BOLD activations were more widespread, but spatially concordant with seizure onset, similar to previous reports of ictal EEG-fMRI in focal epilepsy (Kobayashi, Hawco et al. 2006, Tyvaert, Hawco et al. 2008). Although the areas of activation were more widespread than the resected area, it is notable that the area of most significant early ictal correlated positive BOLD signal change was within the resected tissue in both cases, an effect which I evaluated further in a larger group of patients in subsequent experiments (chapter 7).

A limitation of this study is the assumption that the EEG recorded during scanning is typical for the patient in question as well as the reliance on experienced observers for the identification of events. One study has highlighted the issue of observer bias in EEG-fMRI and noted that misidentification or mis-timed event markers could result in variability in the number of statistically significant voxels in a region of BOLD signal change (Flanagan, Abbott et al. 2009), although the results of other studies suggest that results obtained from IED-related BOLD analysis are reproducible meaning that his problem is perhaps not relevant if expert EEG analysis is employed (Gholipour, Moeller et al. 2010). In addition, previous work by my colleagues suggests that EEG quality during scanning is adequate and that IEDs were accurately identified when assessed by two observers (Salek-Haddadi, Lemieux et al. 2003). Further work has subsequently been undertaken which suggests that sensitivity could be improved by
the use of voltage maps derived form high quality out of scanner EEG and mapped onto the intra-scanner recording which may be a more reliable measure of inter-EEG validity (Grouiller, Thornton et al. 2011).

5.4.3 Deactivations

This study focused on positive BOLD signal change, similar to previous investigations which assessed concordance of BOLD signal change and seizure focus. BOLD signal decrease was observed remote from the seizure onset zone in 7/10 cases. This work did not focus on BOLD ‘deactivations’ which evidence suggests may be represent regions functionally connected with the irritative zone and reflect neuronal inhibition (Shmuel, Augath et al. 2006). Deactivations in these cases were predominantly limited to the contralateral hemisphere and the ‘default mode network’, similar to previous reports of IED associated EEG fMRI in both primary generalised (genetic) epilepsies and focal epilepsy (Archer, Abbott et al. 2003, Hamandi, Salek-Haddadi et al. 2006, Kobayashi, Bagshaw et al. 2006, Laufs, Hamandi et al. 2007, Fahoum, Lopes et al. 2012).

5.4.4 Non-resected group

In 24 patients resection was not carried out including 11 who had activations on EEG-fMRI. The results are not discussed in detail here, but it is notable that in those patients in whom the seizure onset zone was found to be extensive on intracranial recording, EEG fMRI activations were also generally widespread. It is notable that fewer events were recorded in the group that underwent resection compared to those that did not and in particular a greater proportion of patients who underwent resection had no IEDs compared to those who did not (69% vs. 54% of patients with no IEDs). This reflects the case mix, in particular the higher proportion of patients in the resected
group with mesial temporal lobe epilepsy, in whom fewer IEDs are observed on scalp recordings in general. At the time of this experiment, not all without IEDs had reached one year follow up and so patients who do not have IED-relate BOLD signal change during EEG-fMRI are discussed further in chapters 6 and 10.

5.4.5 Further Work

These results suggest that the EEG-fMRI has potential use as a clinical tool, particularly in the sub-group of patients in whom the EEG is active, but localisation using conventional means is difficult. In the next sections of this thesis I present further work required to establish its validity in larger patient groups with specific syndromes, in particular those undergoing intra-cranial recording and also to identify those sub-groups in whom the technique adds most value to existing methods of pre-surgical assessment. Improvement in EPI acquisition and co-registration between MRI modalities may be able to extend the usefulness of EEG-fMRI as well as the developments in EEG analysis alluded to above. Since this pilot study, other groups (including a collaboration between the Epilepsy Society MRI Unit and Geneva using data from this project) have published post-operative data in small groups of patients, and prospective data in a larger group (see chapter 10) also adds to this data (Grouiller, Thornton et al. 2011, van Houdt, de Munck et al. 2013).

5.5 Conclusion

Results suggest that localisation based on EEG-fMRI of interictal and ictal activity may be a useful adjunct to the pre-operative work up of patients in whom surgery for focal epilepsy is being considered, particularly when standard data does not indicate a clear-cut focus. We demonstrate good concordance of IED-correlated BOLD with the
seizure onset zone and the observation that the presence of IED-correlated BOLD activations remote from the seizure onset zone is associated with poorer outcome is particularly interesting. These findings support the argument that EEG-fMRI may have a valuable role in pre-surgical evaluation in focal epilepsy which is investigated further in the following sections.
6 EXPERIMENT 2: EEG-FMRI REVEALS EPILEPTIC NETWORKS AND IS A USEFUL ADJUNCT TO PRE-SURGICAL EVALUATION IN FOCAL CORTICAL DYSPLASIA

6.1 Summary:

Following the preliminary study presented in Chapter 5, I sought to make a systematic comparison of EEG-fMRI results with icEEG data to assess the potential role of the technique in pre-surgical evaluation. I chose to consider patients with focal cortical dysplasia in the first instance as surgical treatment of focal epilepsy in patients with Focal cortical dysplasia (FCD) is most successful if all epileptogenic tissue is resected, but this may not be evident on structural MRI. EEG-fMRI as a novel non-invasive imaging technique is therefore, of particular interest in this group. The following experiment aimed to assess the value of EEG-fMRI in patients with focal epilepsy and FCD by testing whether IED-related haemodynamic changes could predict the SOZ on icEEG and also whether those changes which lie outside of the SOZ have any relationship to the icEEG and post-operative outcome.

Methods:

All patients with FCD were selected from the cohort recruited as described in section 2.1 and those that had undergone icEEG and reached one year post-operative follow up were analysed for this experiment. IEDs recorded during scanning were used to model haemodynamic changes throughout the brain. The results were overlaid on co-registered T1-weighted MRI scans, fused with individual CT scans following implantation of intracranial electrodes. Regions of haemodynamic change were compared with the irritative zone (IZ) and SOZ identified on icEEG, and the degree of
concordance and the relationship between the degree of concordance and post-operative outcome in those patients who underwent surgical resection were assessed.

Results:

23 patients had focal cortical dysplasia diagnosed on structural MRI, post-operative histology or both and had reached the required follow up period at the time of the experiment. 12/23 patients had IEDs during recording. 11/12 patients had significant IED related haemodynamic change. Widespread, bilateral changes were observed in 4/11 patients of whom 3 had a multifocal SOZ on icEEG. 5/11 had unilateral changes with at least one cluster concordant with the SOZ which was unifocal in 4/5 on icEEG. In 2 patients the IED-related haemodynamic change consisted of a single cluster concordant with the SOZ.

Conclusion:

EEG-fMRI may provide useful additional information about the SOZ and IZ in FCD. In particular, widely distributed regions of IED-related haemodynamic change appear to be associated with a multifocal SOZ on icEEG and a lower chance of seizure freedom following surgical resection.
6.2 Introduction

Focal Cortical Dysplasia (FCD) describes a group of abnormalities in the structure of the cortex, originally classified by Palmini (Palmini, Najm et al. 2004) but updated recently (Blümcke, Thom et al. 2011), resulting from abnormal neuronal migration which may occur prenatally or early in life, and commonly associated with epilepsy (Palmini, Gambardella et al. 1995). FCD associated epilepsy is pharmaco-resistant in many cases and surgical treatment may be considered, often requiring intracranial EEG recordings to localise the region of seizure onset and to map eloquent cortex. Recently the classification of these abnormalities has been revisited and the clinical significance of these sub-types is now being evaluated as discussed in section 2.6.3.2 (Blümcke, Thom et al. 2011).

Intracranial EEG studies have challenged the idea that epilepsy in FCD typically has one seizure onset zone colocalised with the lesion and suggested that there may be discrete dysplastic foci as well as structurally normal remote cortical areas exhibiting epileptogenicity (Fauser, Sisodiya et al. 2009) (Aubert, Wendling et al. 2009). The presence of highly ‘epileptogenic’ remote from the region of dysplasia are reported to be associated with poorer outcome, consistent with Magnetoencephalography (MEG) studies (Widjaja, Otsubo et al. 2008). Whilst FCD is frequently seen on structural MRI, particularly type 2B, in a significant number, current structural MRI may appear normal (Tassi, Colombo et al. 2002, McGonigal, Bartolomei et al. 2007) and so there is a need for better evaluation of the involvement of distributed epileptogenic foci.

Simultaneous EEG-fMRI recordings have been used to study haemodynamic changes over the whole brain associated with interictal discharges (IED), and there is increasing interest in the potential clinical role of the technique (further details in section 2.13.4.). There are several case reports and small series using EEG-fMRI in patients with FCD,
in which it was noted that clusters of IED-correlated BOLD were both local to and remote from the seizure onset zone, including sub-cortical structures (Federico, Archer et al. 2005) (Tyvaert, Hawco et al. 2008), but these changes have not been compared with icEEG in a systematic way.

Assessment of the relationship between IED-correlated fMRI results and intracranial EEG, have generally been limited to case descriptions in the context of broader studies of patients with epilepsy of mixed aetiology and there is a small, but increasing, body of evidence regarding the clinical utility of EEG-fMRI in pre-surgical evaluation (Zijlmans, Huiskamp et al. 2007) (Thornton, Laufs et al. 2010) (see section 2.13.4 for a more detailed discussion and evidence presented in sections 5 and 10).

In this experiment, I sought to build on these findings in the light of increasing evidence from both invasive EEG and imaging studies that FCD contributes to an epileptic network rather than being a discrete epileptic focus, which has implications for successful surgical treatment (Aubert, Wendling et al. 2009) (Eriksson, Rugg-Gunn et al. 2001). To this end I aimed to evaluate EEG-fMRI in the assessment of patients with FCD by prospectively comparing IED-related BOLD signal changes with the results of invasive EEG (icEEG) in patients undergoing pre-surgical evaluation. I aimed to assess whether regions of IED related BOLD signal change are meaningful representations of epileptogenicity in FCD with potential implications for surgical efficacy where multiple regions of signal change were detected. In addition I attempted to observe if there was any association between the extent of IED related BOLD signal change and post-operative outcome.
6.3 Materials and methods

6.3.1 Patients

The patients were selected from the cohort described in section 3.1.1. At the time of this experiment 65 of whom 23 had a diagnosis of Focal Cortical Dysplasia made on structural MRI, histology or both had been scanned and reached at least one year post-operative follow up. All underwent intracranial EEG. Post-operative outcome was recorded at 12 months using the International League Against Epilepsy rating scale (Wieser, Blume et al. 2001)

For this analysis, in order to given meaningful clinical data, surgical outcome was considered good if there was a reduction of >50% in seizure days (ILAE 1-3) and poor if there was less than a 50% reduction in seizure days (ILAE 4-6).

Procedures were subject to the appropriate ethics and consents described in Chapter 3.

6.3.2 Electroclinical evaluation

All patients underwent electro-clinical evaluation according to local protocol as described in section 3.1.3. Structural MRI was undertaken at 3T according to the National Society for Epilepsy Protocol described in section 3.1.3. Each patient subsequently underwent intracranial EEG with an individually tailored electrode implantation, determined by the clinical team at the patient’s centre using sub-dural grids, depth electrodes or a combination of both according clinical need and local protocol. EEG-fMRI scans were not used in the planning of icEEG or subsequent resection.
6.3.3 EEG-fMRI Acquisition

Each patient underwent EEG-fMRI scanning for 40-60 minutes as described in section 3.1.4.

6.3.3.1 EEG pre-processing

EEG pre-processing was undertaken as described in section 3.1.5 and IEDs marked by two observers (myself and S.Vulliemoz, S. Cannadathu or A. Vaudano). IEDs were also compared with those recorded during video-EEG to ensure they were representative of the patient's usual observed interictal activity.

6.3.3.2 fMRI analysis

fMRI pre-processing and general linear model analysis was undertaken for IEDs as described in section 3.1.6. Motion-related effects were included in the GLM as 24 regressors (Volterra expansion of the 6 scan realignment parameters and of the previous volume). An additional set of confound regressors was included to account for cardiac pulse-related signal changes (Liston, Lund et al. 2006).

6.3.3.3 Comparison of the EEG-fMRI results with intracranial EEG

Patient-specific T1-weighted MRI scans obtained during the EEG-fMRI recording were co-registered and fused with a post-implantation CT with the sub-dural grid or depth electrodes in situ (Winkler, Vollmar et al. 2000). These fused images were co-registered with the SPM{F} to identify regions of BOLD signal change in relation to the intracranial EEG. The degree of concordance of the GLM results was assessed based on the entire statistical maps and summarised as either:
**Concordant (C),** when all significant BOLD clusters were concordant with the site of seizure onset identified on intracranial EEG, defined when the area of maximal signal change was in the same lobe and within 2cm of the intracranial EEG electrode marking seizure onset.

**Concordant+ (C+)** when one the most significant BOLD signal cluster was concordant but additional, remote statistically significant clusters were also revealed within or bordering the same lobe,

**Discordant+ (D+)** when significant cluster(s) were concordant with the seizure onset zone, but additional widespread clusters were observed outside of the same lobe,

**Discordant (D),** when no cluster was concordant

**NULL,** when no significant activation was revealed.

This represents a change from our previous concordance classification system following recent evidence from our simultaneous electrical source imaging and fMRI which demonstrated that the cluster which contains the global statistical maximum may correspond to the seizure onset zone or a region of spike propagation (Vulliemoz, Thornton et al. 2009). The classification was made irrespective of the sign of the BOLD signal change. The location of all observed clusters of BOLD signal change was assessed in relation to the irritative zone (IZ), the area of cortex giving rise to inter-ictal discharges and seizure onset zone (SOZ), the area of cortex where the seizure begins on icEEG (Rosenow and Luders 2001). I have restricted my definition of ‘concordant clusters’ to clusters lying within 2cm of the electrodes overlying the seizure onset zone based on observations of potential inter-modality co-registration inaccuracies and measures of intra-operative cortical displacement described in previous studies (Nimsky, Ganslandt et al. 2000).
6.4 Results

Electro-clinical data can be found in Table 6.1. The EEG-fMRI results are given in Table 6.2. Figures 6.1, 3 and 4 show illustrative cases (patients #3, #19 and #22 respectively). Details of each patient’s icEEG recording is given in Table 6.3. Illustrative figures showing schematics of the icEEG implantation and typical ictal and interictal activity can be found in figures 6-1 and 2.

6.4.1 EEG-fMRI Results

12/23 had IEDs during EEG-fMRI scanning of whom 11 had significant BOLD signal change related to the IEDs recorded during scanning. The EEG-fMRI and icEEG results are summarised in Table 6.3. In 10/11 patients, only one type of IED similar to that seen on long term video EEG yielded significant IED-related BOLD signal change, although more than one type was observed in patients 2, 3, 9 and 20. In patient 2, the second type of IED was not observed on the patient’s routine investigation (left frontal fast in patient 2 was only seen at seizure onset during video telemetry) and in patients 3 and 9 the second type of IED was not associated with BOLD signal change. In patient 20, 2 types of IED (spikes and polyspikes), were associated with multiple clusters of widespread BOLD signal change.

2/11 patients were classified concordant (C) (patients #18 and 21), 4/11 were classified concordant + (C+) (patients #3, 9, 19 and 22), 3/11 were classified discordant + (D+) (#1, 12 and 20) and the remaining 2/11 patients was classified D (#2 and 23) when EEG-fMRI results were compared with icEEG.
Table 6.1 Clinical details of patients with a diagnosis of Focal Cortical Dysplasia at one year post-operative follow up

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy</th>
<th>MRI</th>
<th>Scalp EEG</th>
<th>Semiology</th>
<th>icEEG (centre)</th>
<th>IZ (icEEG)</th>
<th>SOZ (icEEG)</th>
<th>Resection</th>
<th>Histology</th>
<th>Outcome (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LFLE</td>
<td>FCD L SFG</td>
<td>LF ShW</td>
<td>R hand motor seizures</td>
<td>LF gr and depth (N)</td>
<td>Post L SFG</td>
<td>Post L SFG</td>
<td>None (P)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>LFLE</td>
<td>FCD L SFG</td>
<td>LT ShW, LF poly</td>
<td>Behavioural arrest, R arm clonus</td>
<td>LF gr and depth (N)</td>
<td>L MFG and IFG</td>
<td>Anterior L MFG</td>
<td>L MFG</td>
<td>FCD 2b</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>LFLE</td>
<td>normal</td>
<td>LF SpW</td>
<td>Behavioural arrest, R head version</td>
<td>LF and LT gr (N)</td>
<td>L MFG, SFG, PCG and IFG</td>
<td>L MFG</td>
<td>L MFG</td>
<td>FCD 2b</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>LFLE</td>
<td>FCD L MFG</td>
<td>LF slow</td>
<td>R arm pulling sensation</td>
<td>LF gr (B)</td>
<td>Post L MFG</td>
<td>Post L MFG</td>
<td>L MFG</td>
<td>FCD 2a</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>LFLE</td>
<td>FCD L MFG</td>
<td>LF slow</td>
<td>R sensori-motor seizure</td>
<td>LF gr and depth (N)</td>
<td>L MFG and IFG</td>
<td>L MFG</td>
<td>L MFG</td>
<td>FCD 2b</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>RFLE</td>
<td>FCD RF</td>
<td>RF slow</td>
<td>Sensation of legs moving</td>
<td>RF gr and depth to lesion (N)</td>
<td>R prim motor cortex</td>
<td>R prim motor</td>
<td>None (Sz)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>RFLE</td>
<td>normal</td>
<td>normal</td>
<td>L motor seizure</td>
<td>RF gr and depth (N)</td>
<td>R prim motor cortex</td>
<td>R prim motor cx</td>
<td>None (P)</td>
<td>FCD 2b</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>RFLE</td>
<td>FCD R Pre-C</td>
<td>RC slow</td>
<td>L leg motor seizure</td>
<td>RF-P gr (N)</td>
<td>R prim motor cx</td>
<td>R prim motor and sensory cx</td>
<td>None (P)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>ROTPL</td>
<td>FCD R</td>
<td>RT poly, Behavioural arrest,</td>
<td>sEEG (MF)</td>
<td>RT lobe</td>
<td>RT lobe (basal)</td>
<td>R mTLob</td>
<td>FCD 2b</td>
<td>4*</td>
<td></td>
</tr>
</tbody>
</table>

L=left, R=right, F= frontal, T= temporal, P= parietal, O= occipital, C= central, post= posterior, ant= anterior, S= superior, I= inferior, M= middle, G= gyrus. SpW= spike and wave complex. ShW= sharp wave, Gr= sub-dural grid, Strip= sub-dural strip, depth= depth electrode (between 6 and 15 contacts per electrode), m= mesial, prim= primary, cx= cortex IZ= Irritative zone, SOZ= seizure onset zone, icEEG= intracranial EEG. FCD= Focal Cortical Dysplasia. Resections: Lob=lobectomy. All others refer to anatomical location of resection. None= resection was contra-indicated owing to proximity to eloquent cortex (E) or poorly localised seizure onset (Sz). Centres: N= National Hospital for Neurology and Neurosurgery, UK, B= North Bristol Hospital, UK, K= Kings College Hospital, UK, MF= Hopital de la Timone, Marseille, France.*Restricted resection to avoid visual field defect following discussion with patient.
<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>(T,P,O)</th>
<th>RT-P</th>
<th>hypermotor</th>
<th>(extensive)</th>
<th>mesial</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>RTLE</td>
<td>FCD R STG</td>
<td>RT and LT ShW</td>
<td>Behavioural arrest, manu</td>
<td>RT strips (K)</td>
<td>L post TL</td>
<td>L post STG</td>
<td>None (Sz)</td>
</tr>
<tr>
<td>11</td>
<td>RPLE</td>
<td>FCD RO</td>
<td>RP slow</td>
<td>Behavioural arrest</td>
<td>RO and RP gr (N)</td>
<td>R PL and OL (extensive)</td>
<td>R PL</td>
<td>None (Sz)</td>
</tr>
<tr>
<td>12</td>
<td>LTLE</td>
<td>FCD L post T</td>
<td>LTP SpW</td>
<td>Oral automatism</td>
<td>LT and LP gr (N)</td>
<td>L TL and PL</td>
<td>L post TL</td>
<td>Lpost TLo</td>
</tr>
<tr>
<td>13</td>
<td>RTLE</td>
<td>normal</td>
<td>RT slow</td>
<td>Oral automatism</td>
<td>RT gr (N)</td>
<td>R lat TL and infr TL</td>
<td>R TL</td>
<td>R mTLo</td>
</tr>
<tr>
<td>14</td>
<td>LTLE</td>
<td>normal</td>
<td>LT slow</td>
<td>LT gr (K)</td>
<td>L TL and PL</td>
<td>L post TL</td>
<td>None (Sz)</td>
<td>FCD sub-type not defined</td>
</tr>
<tr>
<td>15</td>
<td>LTPLE</td>
<td>FCD Post L T</td>
<td>LT ShW</td>
<td>Behavioural arrest, oral automatism</td>
<td>LP gr (N)</td>
<td>LP lobe</td>
<td>LP lobe</td>
<td>L PLo</td>
</tr>
<tr>
<td>16</td>
<td>LPLE</td>
<td>FCD RP</td>
<td>LT and LP SpW</td>
<td>R hand sensory sz</td>
<td>LP gr and depth to lesion (N)</td>
<td>L prim sensory cortex</td>
<td>L prim sensory cortex</td>
<td>FCD 2b</td>
</tr>
<tr>
<td>17</td>
<td>LPLE</td>
<td>FCD LP</td>
<td>LP slow</td>
<td>Weakness R hand</td>
<td>LP gr and depth to lesion (N)</td>
<td>L PLand TL</td>
<td>L prim sensory cortex</td>
<td>None (P)</td>
</tr>
</tbody>
</table>

L=left, R=right, F= frontal, T= temporal, P= parietal, O = occipital, C= central, post = posterior, ant = anterior, S = superior, I = inferior, M = middle, G = gyrus. SpW= spike and wave complex. ShW = sharp wave, Gr= sub-dural grid, Strip = sub-dural strip, depth= depth electrode (between 6 and 15 contacts per electrode), m = mesial, prim = primary, cx= cortex IZ= Irritative zone, SOZ = seizure onset zone, iceEEG= intracranial EEG. FCD= Focal Cortical Dysplasia. Resections: Lob=lobectomy. All others refer to anatomical location of resection. None= resection was contra-indicated owing to proximity to eloquent cortex (E) or poorly localised seizure onset (Sz). Centres: N= National Hospital for Neurology and Neurosurgery, UK, B= North Bristol Hospital, UK, K = Kings College Hospital, UK, MF= Hopital de la Timone, Marseille, France. *Restricted resection to avoid visual field defect following discussion with patient.
<table>
<thead>
<tr>
<th>No</th>
<th>Patient</th>
<th>Stigma</th>
<th>Location</th>
<th>Characteristics</th>
<th>Procedure</th>
<th>Post Op Complications</th>
<th>Other Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>RPLE FCD R Post CG</td>
<td>RC slow</td>
<td>R foot sensory sz</td>
<td>RP gr and depth to lesion (N)</td>
<td>R prim sensory cortex</td>
<td>R mesial prim sensory cortex</td>
<td>R prim sensory cortex</td>
</tr>
<tr>
<td>19</td>
<td>RPLE normal</td>
<td>RP sp wave RC sh wave</td>
<td>R foot clonus</td>
<td>sEEG (MF)</td>
<td>R prim motor and sensory cortex</td>
<td>R prim motor cortex</td>
<td>gamma knife</td>
</tr>
<tr>
<td>20</td>
<td>Bil</td>
<td>FCD R STG &amp; IFG</td>
<td>RP ShW</td>
<td>Behavioural arrest, oral automatism</td>
<td>sEEG (MF)</td>
<td>Bil PL, OL, R TL</td>
<td>Bil PL</td>
</tr>
<tr>
<td>21</td>
<td>ROLE FCD RO</td>
<td>RT ShW</td>
<td>Visual hallucination, loss of awareness</td>
<td>RO gr (B)</td>
<td>R OL, PL, post TL</td>
<td>R OL</td>
<td>R OLob</td>
</tr>
<tr>
<td>22</td>
<td>LOLE FCD LO</td>
<td>LOP ShW</td>
<td>Sensation of eyes pulled to R. Oral automatisms</td>
<td>2x LO grs, str, 2x LO depths (B)</td>
<td>L OL, L mes PL</td>
<td>L OL</td>
<td>L OLob</td>
</tr>
<tr>
<td>23</td>
<td>LNLE FCD L perisylvian</td>
<td>GSW, LT ShW</td>
<td>Loss of awareness, head version (R)</td>
<td>LF gr (N)</td>
<td>L mes FL</td>
<td>L ant SFG</td>
<td>None (Sz)</td>
</tr>
</tbody>
</table>

L=left, R=right, F= frontal, T= temporal, P= parietal, O= occipital, C= central, post = posterior, ant = anterior, S = superior, I = inferior, M = middle, G = gyrus. SpW= spike and wave complex. ShW = sharp wave, Gr= sub-dural grid, Strip = sub-dural strip, depth= depth electrode (between 6 and 15 contacts per electrode), m= mesial, prim = primary, cx= cortex IZ= Irritative zone, SOZ = seizure onset zone, ieEEG= intracranial EEG. FCD= Focal Cortical Dysplasia. Resections: Lob=lobectomy. All others refer to anatomical location of resection. None= resection was contra-indicated owing to proximity to eloquent cortex (E) or poorly localised seizure onset (Sz).Centres: N= National Hospital for Neurology and Neurosurgery, UK, B= North Bristol Hospital, UK, K = Kings College Hospital, UK, MF= Hopital de la Timone, Marseille, France.*Restricted resection to avoid visual field defect following discussion with patient.
Table 6.2 Results of IED-related BOLD signal change, icEEG and post-operative outcome

<table>
<thead>
<tr>
<th>No of IEDs</th>
<th>IED-related BOLD Signal Cluster</th>
<th>Histological diagnosis</th>
<th>Outcome</th>
<th>Seizure onset zone</th>
<th>Concordance with icEEG</th>
<th>Single vs. multifocal (icEEG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM 2nd 3rd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70 Caudate (-)</td>
<td>Left superior frontal gyrus (-)</td>
<td>Right superior frontal gyrus (-)</td>
<td>FCD 2</td>
<td>N/A</td>
<td>Post L SFG</td>
</tr>
<tr>
<td>2</td>
<td>11 Left IFG, STG (+)</td>
<td>Right IFG (+)</td>
<td>FCD 2b</td>
<td>4</td>
<td>Anterior L MFG</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>35 Left middle frontal gyrus (+)</td>
<td>Left IFG/STG, left precentral (+)</td>
<td>DMN (-)</td>
<td>FCD 2a</td>
<td>3</td>
<td>L middle frontal gyrus</td>
</tr>
<tr>
<td>9</td>
<td>82 Right mesial inf temporal (+)</td>
<td>Right postero-lateral temporal (+)</td>
<td>FCD 2b</td>
<td>4*</td>
<td>RT lobe (basal-mesial)</td>
<td>C+</td>
</tr>
<tr>
<td>12</td>
<td>137 Left post T (border of prev resection) (+)</td>
<td>L IFG (+)</td>
<td>L lateral PL and PCC (-)</td>
<td>Not defined</td>
<td>5</td>
<td>L post TL and L parietal lobe (other regions not seen)</td>
</tr>
<tr>
<td>16</td>
<td>201 None</td>
<td>FCD 2b</td>
<td>1</td>
<td>L prim sensory cortex</td>
<td>No IED correlated BOLD</td>
<td>Single (small IZ)</td>
</tr>
</tbody>
</table>

Abbreviations: IED = interictal epileptiform discharge, L=left, R=right, F= frontal, T= temporal, P= parietal, O = occipital, C= central, post = posterior, ant = anterior, S = superior, I = inferior, M = middle, G = gyrus, m = mesial, prim = primary, cx= cortex IZ= Irritative zone, SOZ = seizure onset zone, icEEG= intracranial EEG, C = Concordant, C+ = concordant +, D = discordant, D+ = discordant + (see main text).
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2*</td>
<td>Right pre and post central gyri (+)</td>
<td>FCD 2a</td>
<td>1</td>
<td>R mesial prim sensory cortex</td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>Right medial pre-central gyrus (+)</td>
<td>Right middle frontal gyrus (+)</td>
<td>2</td>
<td>R prim motor cortex</td>
</tr>
<tr>
<td>20</td>
<td>61</td>
<td>Right frontal: extensive (+)</td>
<td>Left MFG (+)</td>
<td>Right lat TP border(-)</td>
<td>N/A (poor)</td>
</tr>
<tr>
<td>21</td>
<td>123</td>
<td>Right mesial occipital (+)</td>
<td>Right lateral occipital</td>
<td>FCD 3</td>
<td>4</td>
</tr>
<tr>
<td>22</td>
<td>12</td>
<td>Mesial occipital (+)¹</td>
<td>Left mesial occipital (+)¹</td>
<td>FCD 2b</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>89</td>
<td>post-central gyrus (+)</td>
<td></td>
<td>N/A (poor)</td>
<td>R parietal</td>
</tr>
</tbody>
</table>

Abbreviations: IED = interictal epileptiform discharge, L=left, R=right, F=frontal, T= temporal, P= parietal, O= occipital, C= central, post = posterior, ant = anterior, S = superior, I = inferior, M = middle, G = gyrus, m = mesial, prim = primary, cx= cortex IZ= Irritative zone, SOZ = seizure onset zone, icEEG= intracranial EEG, C = Concordant, C+ = concordant +, D = discordant, D+ = discordant + (see main text).
Table 6.3 Details of intracranial EEG

<table>
<thead>
<tr>
<th>Seizure onsets zone</th>
<th>Implantation details</th>
<th>Seizure onset and propagation (rapid propagation = &lt;0.5 seconds from onset)</th>
<th>Interictal discharges (IZ)</th>
<th>Resection Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relationship to BOLD signal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Histology/ size</td>
</tr>
<tr>
<td>1</td>
<td>Post L SFG</td>
<td>32c Gr (Gr 1-32) over L FP convexity, 6c depth (D1-6) to lesion (sup FG)</td>
<td>Fast activity D4-6, Gr 11 overlying lesion.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D4-6, Gr 11,12,18,19 (cortex overlying lesion in LSFG)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Anterior L MFG</td>
<td>32c Gr (Gr 1-32) over L lateral F convexity, 6c depth to lesion in L MFG</td>
<td>Fast activity anterior grid spreading to D5-6</td>
<td>Anterior LF resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sup grid (anterior and post contacts)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6x4cm</td>
</tr>
<tr>
<td>3</td>
<td>L middle F gyrus</td>
<td>48c Gr (Gr1-48) over L lateral F convexity, 16c Str (2Gr 1-16) over L IFG and L STG. 2x depths (DA1-6, DP1-6)</td>
<td>Fast activity post-sup quadrant of grid overlying lesion. Rapid propagation to precentral gyrus</td>
<td>LF corticectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sup-post grid, sup strip overlying LIFG, lateral contacts of DA.</td>
<td>Included cluster containing GM.</td>
</tr>
<tr>
<td>9</td>
<td>RT Lo (basal- sEEG; 10x 10c depths to right hemisphere</td>
<td>Fast activity mesial contacts RH depth R</td>
<td>RH depth (mes contacts), R basal T</td>
<td>R ATL (partial as</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Included cluster containing GM.</td>
</tr>
</tbody>
</table>

Abbreviations:
- R=right, L=left, F=frontal, O=occipital, T=temporal, P=parietal, Post=posterior, ant=anterior, sup=superior, M=middle, inf=inferior, mes=mesial, H=hippocampal, G=gyrus, GM=global maximum, FCD=focal cortical dysplasia,
- Gr=sub-dural grid, c=contact, sEEG=stereo-electroencephalography (depths only), D=depth electrode, Str=sub-dural strip electrode
<table>
<thead>
<tr>
<th>Area</th>
<th>Description</th>
<th>Activity</th>
<th>Location</th>
<th>Extent</th>
<th>Other</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>L post T and LP (likely</td>
<td>32c Gr (Gr1-32) over L temporo-parietal convexity, post to previous resection margin. 1x F 8c</td>
<td>Fast activity over post-inf quadrant of grid (Gr1-4, 9-13) propagates</td>
<td>Post half of grid and LT strip</td>
<td>Extension of previous resection margin</td>
<td>None</td>
<td>2.3x3.1cm, normal hippocampus</td>
</tr>
<tr>
<td>other regions not seen)</td>
<td>strip (LF 1-8), 1x temporal 8c strip (LT1-8)</td>
<td>sup and anteriorly Post half of grid and LT strip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>Fast activity over post-inf quadrant of grid (Gr1-4, 9-13) propagates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L prim sensory cortex</td>
<td>48c Gr (1-48) over L temporo-parietal convexity</td>
<td>Fast activity and spikes building up over lesion</td>
<td>As SOZ</td>
<td>Lesionectomy</td>
<td>N/A</td>
<td>FCD 2b, fragmented</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R medial prim sensory</td>
<td>64c grid over pericentral cortex. 2x 6c depths to mesial post-central gyrus (DA1-6) and mesi</td>
<td>Fast activity and spikes over lesion and lateral 2 contacts of anterior</td>
<td>As SOZ</td>
<td>Lesionectomy</td>
<td>Included area of max signal change</td>
<td>FCD 2b, 4x 3.3 cm, clear resection margin</td>
</tr>
<tr>
<td>cortex</td>
<td>mesial post-central gyrus (DA1-6) and mes parietal lobe (DP1-6)</td>
<td>depth (mes contacts), RO and RP depths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>risk of visual field defect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviations: R=right, L=left, F=frontal, O=occipital, T= temporal, P= parietal, Post= posterior, ant= anterior, sup= superior, M = middle, inf= inferior, mes= mesial, H= hippocampal, G= gyrus, GM= global maximum, FCD = focal cortical dysplasia, Gr= sub-dural grid, c= contact, sEEG= stereo- electroencephalography (depths only), D=depth electrode, Str= sub-dural strip electrode</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>19</td>
<td>R prim sensori-motor cortex</td>
<td>sEEG: 3x 15c transverse electrodes (R pre-motor cortex, R pre-central gyrus, R parietal), 1x 15c oblique electrode (R medial pre and post central gyrus)</td>
<td>Fast activity and repetitive spikes over mesial and lateral contacts of R pre-central depth.</td>
<td>Medial contacts and lateral contacts R pre-central, R SMA depths</td>
<td>Gamma knife R pre-central gyrus</td>
<td>Gamma knife in region of max signal change. Additional cluster in the same lobe.</td>
</tr>
<tr>
<td>20</td>
<td>R TPO junction L TPO junction R F</td>
<td>sEEG: 9x 15c depth electrodes (R, T, P and O lobes) 1x15c depth electrode (LP)</td>
<td>Independent foci of fast activity building in R and L fusiform gyrus mesial contacts</td>
<td>Widespread spikes RT, RP and LP depth electrodes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>21</td>
<td>R OL</td>
<td>32c Gr R medial occipital, 16c strip R med Occ.</td>
<td>Fast activity building over infero-mesial contacts of L mes occ grid. Rapid spread to R hemisphere</td>
<td>R mes occipital Gr c2-16</td>
<td>Limited R occipital lobe resection (to avoid visual field defect)</td>
<td>Included area of max signal change</td>
</tr>
</tbody>
</table>

Abbreviations: R=right, L=left, F=frontal, O=occipital, T=temporal, P=parietal, Post=posterior, ant=anterior, sup=superior, M=middle, inf=inferior, mes=mesial, H=hippocampal, G= gyrus, GM=global maximum, FCD=focal cortical dysplasia, Gr=sub-dural grid, c=contact, sEEG=stereo-encephalography (depths only), D=depth electrode, Str=sub-dural strip electrode
<table>
<thead>
<tr>
<th></th>
<th>L medial occipital, 20c Gr L temporoparietal, 16c Str, L med occipital</th>
<th>Repetitive spikes and fast activity over mesial contacts lateral occ grid. Rapid propagation to R mes occ strip</th>
<th>L lateral occipital grid (widespread)</th>
<th>L occipital lobe resection</th>
<th>Included area of max signal change. Additional cluster in the same lobe</th>
<th>FCD 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>L medial</td>
<td>20c Gr L lateral occipital, 20c Gr L temporoparietal, 16c Str, L med occipital</td>
<td>Repetitive spikes and fast activity over mesial contacts lateral occ grid. Rapid propagation to R mes occ strip</td>
<td>L lateral occipital grid (widespread)</td>
<td>L occipital lobe resection</td>
<td>Included area of max signal change. Additional cluster in the same lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>R parietal</td>
<td>64c Gr R TPF, depths to R post T (RPT 1-8) and RP (RP1-6)</td>
<td>Unclear</td>
<td>Sup Gr and RPT depth lateral contacts</td>
<td>None</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations:
R=right, L=left, F=frontal, O=occipital, T=temporal, P=parietal, Post=posterior, ant=anterior, sup=superior, M=middle, inf=inferior, mes=mesial, H=hippocampal, G=gyrus, GM=global maximum, FCD=focal cortical dysplasia, Gr=sub-dural grid, c=contact, sEEG=stereo-electroencephalography (depths only), D=depth electrode, Str=sub-dural strip electrode
6.4.2 Relationship of BOLD signal change to resection and outcome

Both patients with a single BOLD cluster concordant (C) with the SOZ on icEEG were seizure free 12 months after resection (ILAE outcome 1).

Of the patients classified C+, 3/4 (cases #3, 19 and 22) had a good outcome (ILAE 1-3) while remaining patient had a tailored resection to avoid a visual field defect and had a poor outcome (ILAE 4).

Of the patients classified D+, 1/3 (patient #1) did not undergo resection despite a highly localised single seizure focus owing to overlap of the seizure onset zone with primary motor cortex. The remaining 2/3 (patients #12 and 20) patients all had a poor outcome following surgery as the seizure onset zone was widespread (#12) or there were multiple independent sites of seizure onset (#20).

6.4.3 IED-correlated BOLD decreases

In patient #1, all observed clusters of IED related BOLD signal change were decreases including that which was concordant with the seizure onset zone on icEEG. This was the only patient in whom the region of BOLD signal change concordant with the seizure onset zone was negative. In patients # 3, 12 and 20 BOLD decreases were observed in regions of the ‘default mode network’ (Raichle, MacLeod et al. 2001).

6.4.4 Patients with no IEDs during EEG-fMRI.

In 11/23 patients, no IEDs were recorded during EEG-fMRI. Of these patients, 8 had a single focus of seizure onset on icEEG, while a widespread IZ and/or multi-focal SOZ was observed in the remaining 3. 6/8 either had good seizure outcome (ILAE 1-3) or the surgery was precluded despite a single seizure focus owing to overlap with
eloquent cortex. In the remaining 2/8 and those with a multifocal SOZ, outcome following surgery was poor (ILAE class 4-6).

6.4.5 Representative cases

Patient 3 (Figure 6-1 and Figure 6-2) 28-year old female (Patient 3) with normal structural MRI and focal epilepsy (age of onset, 12 years).

Seizures: 3-4 per week, behavioural arrest, right head version, loss of awareness

Scalp EEG: Interictal: left (L) frontal spike wave complexes (maximal, F3) with a wide field Ictal: Left then rapidly generalized, rhythmic spike and wave complexes.

Intracranial EEG: The patient underwent intracranial recording with a 48-contact grid placed over the lateral convexity of the left frontal lobe and a 16-contact grid placed over the left temporal lobe.

Resection: The patient underwent resection of the entire seizure onset zone (but not the region underlying electrodes in the irritative zone). ILAE outcome 3 at 1 year (50% reduction in seizures).

Patient 19 (Figure 6-3) 20 year old male patient with normal structural MRI and focal epilepsy (age of onset 11 years)

Seizures consisted of left foot sensory disturbance followed by left foot clonus and then bilateral arm and leg extension. He had a history of episodes of epilepsia partialis continua of the left foot.

EEG: scalp EEG showed persistent right frontal and central discharges (max F4 and C4). Ictal scalp EEG was similar. Intracranial EEG: the patient underwent icEEG recording with sEEG (4 15 contact electrodes, 3 transverse to R parietal, R SMA and R
OF cortex and a further oblique electrode passing through the pre and post central gyri on the right).

Resection: The patient underwent radiosurgery for a focal abnormality in the right pericentral region. ILAE outcome 5 at 12 months.

Patient 22 (Figure 6-4) 21-year-old male patient with normal structural MRI and focal epilepsy (age of onset, 9 years).

Seizures consisted of a visual aura followed by a sensation of the eyes pulling to the right.

ScalpEEG: Interictal EEG revealed left (L) temporal spikes and sharp waves (maximal, F3–F7). Some more posterior IEDs were recorded during video telemetry, but these were not recorded during scanning. Ictal scalp EEG did not change.

Intracranial EEG: The patient underwent intracranial recording with a 20-contact lateral occipital grid and 16-contact mesial occipital grid in addition to 2 × 6-contact occipital depth electrodes.

Resection of the seizure onset zone, close to the left occipital pole, following which he was seizure free (ILAE outcome 1a at 12 months)
Figure 6-1 EEG-fMRI results compared with icEEG

Patient 3. A. IED-related BOLD signal change overlaid on EPI. Crosshair at global maximum (p<0.05 FWE, z = 7.10). B. Representative epoch of scalp EEG showing left frontal IEDs. C. Time course of haemodynamic change associated with IEDs in B. D. IED-related BOLD signal change overlaid on 3d rendering of fused structural MRI and CT of ic electrodes. Electrodes coded as follows; red= SOZ, orange = rapid propagation (<2 seconds from onset), yellow = IZ.
Figure 6-2 Example of icEEG implantation and recording

Patient 3: (sub-dural grid approach) A. Schematic of implantation, red = seizure onset zone, orange = region to which seizure propagated (<2 seconds), yellow = irritative zone. B. IED related BOLD signal change (purple) overlaid on fused T1-weighted MRI with CT with electrodes in situ. C. Example of a typical seizure in this patient.
Figure 6-3 Example of icEEG implantation and recording

Patient 19 (sEEG approach) A. Schematic of implantation. B Typical interictal activity recorded on icEEG. C. IED-related BOLD signal change (purple) overlaid on fused T1 weighted MRI and CT with electrodes in situ.
Figure 6-4 Patient 22,

A. IED related BLD signal change overlaid on EPI. B. Representative of scalp EEG showing left temporal IEDs. C. Time course of haemodynamic response associated with IEDs in B. D. IED-related BOLD signal change overlaid on 3d rendering of fused T1 weighted MRI and CT with intracranial electrodes in situ.
6.5 Discussion

6.5.1 Main findings of this experiment

This is the first prospective systematic evaluation of the potential role of EEG-fMRI in the pre-surgical evaluation of patients with focal cortical dysplasia by systematic comparison with intracranial EEG. When IEDs were recorded, EEG-fMRI identified regions of IED-related BOLD signal change in 11/12 cases, which represents higher yield than previously reported in studies of EEG-fMRI in patients with focal epilepsy. The results demonstrate that when IEDs were recorded, EEG-fMRI revealed at least one IED related BOLD signal cluster concordant with the seizure onset zone in the majority of cases and was able to detect a previously unidentified seizure focus 2/11 cases, in agreement with previous studies of mixed pathologies and non-sessional cases in focal epilepsy (Zijlmans, Huiskamp et al. 2007, Moeller, Tyvaert et al. 2009).

Results also show that when more than one cluster was present, ‘secondary clusters’ in the ipsilateral hemisphere, and particularly the same lobe often colocalised with the irritative zone on icEEG in cases where a single seizure focus was identified. When multiple clusters of positive IED-related BOLD signal change were identified remote from, and particularly contra-lateral to, the primary seizure focus, multiple epileptic foci were seen on intracranial recording, precluding successful resective surgery. This suggests that IED-related EEG-fMRI can add information to the standard pre-surgical evaluation of FCD and specifically that when multiple widespread clusters of IED-related BOLD activation are identified, there is an increased likelihood of finding a widespread irritative zone or epileptic foci remote from the region of dysplasia. Hence EEG-fMRI may be able to provide useful information regarding the likely success of intracranial EEG evaluation and subsequent surgery in FCD. This supports the pilot
study presented in section 5 which suggested that the presence of widespread positive IED-related BOLD signal clusters pre-operatively was associated with a poor outcome following resection (Thornton, Laufs et al. 2010).

6.5.2 Neurophysiological significance

6.5.2.1 Relationship to recent studies

Recent evidence from studies of intracranial EEG and post-operative outcome in malformations of cortical development have indicated that FCD is not always a discrete lesion and moreover, when it is anatomically discrete, there may be remote regions of structurally normal cortex which also exhibit epileptogenic potential (Aubert, Wendling et al. 2009, Fauser, Sisodiya et al. 2009). These results support the evidence that FCD may be associated with multiple areas of epileptogenicity, and corroborate EEG-fMRI studies including work undertaken during the course of this thesis which demonstrated that IED-related BOLD signal change are observed at the same site and remote from the putative seizure onset zone in malformations of cortical development (Federico, Archer et al. 2005, Kobayashi, Bagshaw et al. 2006, Tyvaert, Hawco et al. 2008).

There was not much variability in IED-related BOLD signal change within the lesion as noted in the largest of these studies (Kobayashi, Bagshaw et al. 2006), which may be as the lesions studied there were grey matter heterotopia and more widespread than the discrete lesions in this study. The observation of IED-related regions of BOLD signal change within the same lobe and remote from the seizure onset zone, concordant with the IZ on icEEG supports ESI studies, which suggest that EEG-fMRI may be a useful tool to image the so-called ‘epileptic network’ (Vulliemoz, Rodionov et al. 2009).
The results are also consistent with previous studies which assume that regions of IED-related BOLD signal change reflect areas of epilepsy related neuronal activity or inhibition (Stefanovic, Warnking et al. 2005) because the clusters were generally associated with epileptogenic tissue on icEEG.

6.5.2.2 Sign of BOLD signal change

I observed IED-related BOLD increases colocalised with the seizure onset zone in 8/9 cases in whom at least one ‘concordant’ cluster was revealed (C, C+ and D+). 71% of clusters remote from the seizure onset zone were also classified as increases. The observation of BOLD decreases colocalised with the seizure onset zone is not new, and various mechanisms for this have been proposed. Recent studies observing haemodynamic change in advance of IEDs suggest that this ‘dip’ may be seen as IED related haemodynamic changes may occur in advance of the IED and that the peak of the canonical HRF may be ‘missed’ by not offsetting the BOLD response (Rathakrishnan, Moeller et al. 2010). A subsequent study comparing this group with icEEG, did not demonstrate a specific icEEG substrate for this (Pittau, Levan et al. 2011). I hypothesize that if this is the case, the fact that a negative response was only observed in a single case may reflect the lesions all being reasonably close to the surface and so scalp EEG is relatively sensitive to these cortical sources compared with deep sources seen in lesions which are in the sub-cortical grey matter (e.g. hippocampal sclerosis), or perhaps that the modeling of the BOLD signal change does not allow for the temporal effects of propagation from deep compared with superficial sources (i.e. volume effects). This is supported by evidence from a group investigating neurovascular coupling in epilepsy who suggest that the negative BOLD response may represent a long undershoot in the HRF and that volume issues should be considered when modeling IEDs (Voges, Blanchard et al. 2012).
Comparison with icEEG suggests that regions exhibiting IED related BOLD increases have a higher proportion of slow EEG frequencies than those with a IED related BOLD decreases (Benar, Grova et al. 2006). The finding that lesional zones often exhibit slow frequency activity correlates well with my observations that most IED related BOLD changes in close proximity to FCD were positive. Although the sign of the change can be variable and requires further investigation these results suggest this does not preclude the possibility of obtaining useful information.

IED-related BOLD decreases were observed in areas suggestive of the Default Mode Network in three patients, in line with previous studies of IED-related BOLD decreases which suggest that this represents a sub-clinical impact on awareness associated with epileptic activity or the reversed causal relationship (Laufs, Hamandi et al. 2007, Vaudano, Laufs et al. 2009). I have not evaluated this effect in detail here.

### 6.5.2.3 Sub-cortical structures

Previous EEG-fMRI studies in malformations of cortical development including FCD report the involvement of the thalamus and basal ganglia in the epileptic network (Federico, Archer et al. 2005) and I observed sub-cortical BOLD signal changes in 3/11 patients. There were no features specific to these patients or the EEG discharges studied compared to others within the group.

### 6.5.3 Clinical Significance

It has been suggested that noninvasive localization techniques such as scalp EEG-fMRI could reduce the need for invasive tests such as icEEG, which remains the gold standard for the localization of epileptic foci, but has significant disadvantages (see section 2.11). Although EEG-fMRI is unable to provide the same information as
icEEG, it benefits from relatively uniform whole-brain coverage. The finding that multiple widespread IED-related BOLD signal clusters were apparently associated with a widespread SOZ or multiple sites of seizure onset suggests a potential use for EEG-fMRI in determining which patients are likely to benefit from icEEG and those in whom results are likely to be poor, an effect which I subsequently assessed in relation to the whole cohort in chapter 10 and which is in agreement with more recent studies suggesting a similar role for EEG-fMRI (Pittau, Dubeau et al. 2012, van Houdt, de Munck et al. 2013).

The size of the group studied here precludes statistically meaningful calculations of sensitivity and specificity with regard to postsurgical outcome. It is of note that in those classified C or C+, surgical outcome was good (ILAE class 1-4) in the majority of cases, whereas surgical outcome was poor (or resection was precluded) in 5 of 6 (83%) of the cases classified D or D+. It should be noted that of those patients classified C or C+, the patients who had the poorest outcomes (ILAE class 5, Patient 19 and ILAE class 4, Patient 21) underwent modified procedures despite a solitary SOZ (gamma knife in Patient 19, meaning 1 year may be too early to assess outcome, and limited resection in Patient 21) to avoid functional deficit. This may explain in part why only 2 of 5 of this group were completely seizure free (ILAE class 1) following resection.

Six of the 11 FCD patients who did not have IED in the EEG-fMRI study had a good seizure outcome. It is not known what BOLD activations would have been found if IED had occurred during these studies. It is evident that the occurrence of IEDs during EEG-fMRI is not in itself a predictive factor for outcome and other measures of epileptic activity are likely to increase the sensitivity of EEG-fMRI (Grouiller, Thornton et al. 2011). It is also evident that in those with FCD, the finding of widespread BOLD
activations with IED appears to be associated with widespread epileptic abnormalities and may be a useful factor to include in the decision to undertake invasive EEG studies.

The finding of IED-related BOLD changes in patients with normal structural MRI is not new (Zijlmans, Huiskamp et al. 2007, Moeller, Tyvaert et al. 2009) but in both MR-negative cases in whom IEDs were recorded in this series (Patients 3 and 22), localization was concordant and surgical outcome was good, providing further evidence of the potential value of EEG-fMRI in the presurgical evaluation of this group.

There was no relationship between the extent of IED-related BOLD changes and histological subtype, although the majority of the patients had FCD type 2.

6.5.3.1 Relationship to Other Non-invasive Modalities.

EEG-fMRI is among several evolving techniques including magneto encephalography (MEG), ESI (used to inform EEG-fMRI), and isotope imaging used in the noninvasive evaluation of epilepsy. MEG appears to have a higher predictive value for surgical outcome and better sensitivity for SOZ localization than PET and SPECT (Knowlton 2006, Knowlton, Elgavish et al. 2008). In a study of MEG in 27 children with FCD, spike sources were detected in all of those with type 2, of whom 46% had clusters concordant with the SOZ (Widjaja, Otsubo et al. 2008). Complete resection of clusters was associated with seizure freedom, but of those with scattered sources, 44% were also seizure free, in contrast to regions of widespread IED-related BOLD signal change, which were usually associated with a poor outcome in our data. Comparison with this small sample suggests that MEG is more sensitive than EEG-fMRI, although when IEDs are recorded in EEG-fMRI, concordant clusters are found in a similar proportion of patients. EEG-fMRI may provide more information about the extent of
epileptic networks than ESI based on a single equivalent dipole model. Comparative
data are required to clarify the roles of each technique, which may provide
complementary information.

6.5.4 Methodological Considerations

6.5.4.1 Limitations of a non-simultaneous study

I cannot comment on the haemodynamic correlates of specific events recorded with
intracranial EEG as the study was not simultaneous so I had to infer that the scalp
EEG recorded during scanning was typical for the patient in question by comparing
each individual’s intra-scan EEG with EEG recorded during pre-surgical evaluation. In
addition, comparison of EEG-fMRI with icEEG suffers from a spatial sampling
mismatch in common with other non-invasive techniques such as MEG and high
density EEG, as it is not a ‘whole brain’ technique. I cannot, therefore comment on
regions of BOLD signal change which did not lie in the vicinity of an electrode.

6.5.4.2 Co-registration

Inter-modality co-registration, particularly between EPI and T1 weighted MRI, as used
here is limited by EPI signal drop-out effects at the brain-CSF-air interfaces (this is
particularly notable close to the frontal sinuses and in the temporal lobes) Intra-
operative cortical shift during electrode placement also occurs which further limits the
accuracy of co-registration in a non-simultaneous study. These factors in addition to
limited spatial resolution, both of icEEG (owing to the distance between electrodes)
and fMRI data (owing to spatial smoothing) contributed to the decision to use a cut-off
of 2cm between seizure onset zone as recorded on icEEG and clusters of IED-related
BOLD signal change for a result to be considered concordant (Nimsky, Ganslandt et al. 2000).

In addition to this, regions of cortical dysplasia do not necessarily lie on the cortical convexity, but may be deep within a sulcus, meaning that there are further potential inaccuracies inferring a quantitative relationship between the seizure onset zone and any clusters of BOLD signal change, an issue which has been addressed by groups who have modeled the surface of the cortex in order to improve the accuracy of measurements (Grova, Makni et al. 2006).

Given these potential sources of error, I used an anatomical description of BOLD cluster localization and degree of concordance rather than a quantitative measure of distance between icEEG contacts and regions of BOLD signal change.

6.5.4.3 Resolution of intracranial EEG

Comparison with icEEG is limited by the fact that although icEEG is the gold standard for seizure onset localization, it does not in reality sample directly from neuronal sources and the problem of source localization (the inverse problem) is not in fact abolished. The definition of the ‘seizure onset zone’ in this experiment refers to that recorded on icEEG. Given these limitations and the limited resolution of macro electrodes (1cm apart), the fMRI resolution should be comparable, as I have used a 8mm smoothing kernel.

6.5.4.4 Confounding factors and yield

EEG-fMRI relies on the recording of events during the scanning period, a limitation shared with both MEG and standard EEG. Events were captured in 47% of the
patients in this group, which may appear relatively low, although previous studies of EEG-fMRI often had a selection bias, considering only patients with a very active resting EEG (Al-Asmi, Benar et al. 2003, Salek-Haddadi, Diehl et al. 2006, Tyvaert, Hawco et al. 2008) in contrast to the prospective study of consecutive cases presented here. No drug reduction was undertaken in this group, which may impact the number of events captured. Approaches to increasing the yield of EEG-fMRI experiments is now underway and indeed the idea of studying IED-related BOLD is likely to become one of a number of possible ways of evaluating ‘epileptic activity’ related BOLD signal change in the future – this will be discussed in more detail in chapter 11.

My approach to fMRI data modelling is designed to ensure that regional BOLD changes explained by confounding factors such as motion and physiological noise are not considered as effects of interest, by incorporating these features in the model.

6.5.5 CONCLUSIONS

These results add to the increasing body of evidence that FCD may be multi-focal with areas of epileptogenic tissue remote from the dysplastic lesion in some cases. I also found that EEG-fMRI may provide useful non-invasive data in some cases, aiding the identification of appropriate patients for icEEG. In particular, the evidence presented here suggests that EEG-fMRI maybe useful in identifying those patients who are more likely to have multiple epileptic foci and are therefore less likely to benefit from icEEG. The size of the group precludes further detailed statistical analysis and a larger pathology specific group with longer follow up may allow this.
7 EXPERIMENT 3: EXPLORING HAEMODYNAMIC CHANGES LINKED TO SEIZURES USING EEG-FMRI: COMPARISON WITH OF GENERAL LINEAR MODEL, INDEPENDENT COMPONENT ANALYSIS AND INTRACRANIAL EEG

7.1 Summary:

Aim:

Here I explored, haemodynamic changes associated with seizures by comparing results obtained using a neurophysiologically informed General Linear Model and data driven analysis of ictal fMRI data. I sought to compare the results with intracranial EEG, which has not previously been done in a systematic way.

Methods:

Nine of 101 patients had seizures during EEG-fMRI and were analyzed using three approaches, a classical general linear model (GLM) using a canonical HRF and information derived from the EEG, a second GLM using a Fourier basis set to allow flexibility in the Haemodynamic response and spatial independent component analysis (ICA) of the fMRI time series. The results were subsequently compared with icEEG.

Results:

The canonical GLM analysis revealed significant BOLD signal changes associated with seizures on EEG in 7/9 patients, concordant with the seizure onset zone in 4/7. The Fourier GLM analysis revealed changes in BOLD signal corresponding with the results of the canonical analysis in two patients. ICA revealed components spatially concordant with the seizure onset zone in all patients (8/9 confirmed by intracranial EEG).
Conclusion:

Ictal EEG-fMRI visualized plausible seizure related haemodynamic changes, which
were spatially concordant with seizure onset on intracranial EEG. The GLM analysis
EEG-fMRI revealed localized BOLD changes concordant with the ictal onset zone
when scalp EEG reflects seizure onset. ICA provided additional information when scalp
EEG did not accurately reflect seizures, and may give insight into ictal
haemodynamics.

7.2 Introduction:

Ictal EEG-fMRI has been carried out in several groups of patients, but such recordings
tend to be obtained fortuitously rather than by design. As has been discussed above,
analysis of ictal EEG-fMRI data has been undertaken using a variety of different
approaches and often reveals clusters of BOLD signal change which are spatially
concordant with the presumed seizure onset as revealed by electro-clinical data
(2.13.6 and 2.13.7).

In most EEG-fMRI studies of ictal activity, seizures are represented as a single block
across their duration convolved with an HRF (see chapter 1.6. 9 for further details). The
approach has several limitations, in particular:

1. Seizure onset may not always be reflected accurately by scalp EEG.
2. A single block may not necessarily be an appropriate model for a seizure, which
   is a complex and evolving event.

In addition to GLM based analyses, several groups have used data-driven approaches
to investigate ictal associated haemodynamic changes, but interpretation of the
resulting components is difficult owing to poor specificity resulting from the number of components identified.

Furthermore, while the canonical HRF appears to be a suitable model in normal physiological conditions (Friston, Frith et al. 1995) and for IED-related BOLD signal changes (Lemieux, Laufs et al. 2008), this has not been demonstrated for seizures. Flexible modeling methods have been used, such as those based on Fourier basis sets (Salek-Haddadi, Diehl et al. 2006) or series of short blocks (Donaire, Falcon et al. 2009, Tyvaert, LeVan et al. 2009) addressing the potential complexity of ictal BOLD signal changes but they do not address the issue of how best to model these changes based on the available scalp EEG.

Given that ictal EEG does not always reflect seizure onset (Binnie and Stefan 1999) providing localizing information in 13–92% of patients (Blume, Luders et al. 2001, Foldvary, Klem et al. 2001) and (Lee, Lee et al. 2005), data driven analysis of fMRI (i.e. without modeling the EEG) may be helpful and has shown haemodynamic change in or near the seizure onset zone associated with seizures (Detre, Sirven et al. 1995, Federico, Abbott et al. 2005). Mathematically rigorous signal processing methods such as independent component analysis (ICA) applied to simulated and interictal data, have demonstrated BOLD changes concordant with the results of traditional EEG-derived fMRI modeling techniques (Rodionov, De Martino et al. 2007, LeVan and Gotman 2009) opening a new avenue for the investigation of seizure-related fMRI changes (LeVan, Tyvaert et al. 2010).

The main objective of the current study was to explore the BOLD signals related to epileptic seizures in a series of patients and compare the resulting patterns of haemodynamic change with subsequent icEEG. I addressed the limitations of a single-
block design GLM, by using two, more flexible modeling approaches:

1. Partition of the seizures into three EEG-defined blocks each convolved with a canonical HRF.
2. Convolution with a Fourier basis set across the entire event for long seizures.

ICA was also combined with an automatic component classifier (De Martino, Gentile et al. 2007) to try and identify seizure specific BOLD signal changes without reference to the EEG. The resulting independent components were assessed by calculation of the correlation between the spatial independent component time courses with the time course of the EEG.

The findings of the three analyses were compared with icEEG.

7.3 Materials and Methods:

7.3.1 Patients Selection

The patients were recruited and electro-clinical data and EEG-fMRI recorded as described in Chapter 3.

Patients were selected for this analysis if they had one or more seizures during the scanning session, determined by patient report, clinical observation and EEG (n = 9).

Eight of nine had subsequent successful intracranial EEG recording to localize the seizure onset zone; in the remaining patient the procedure was abandoned owing to intra-operative complications.
7.3.2 EEG pre-processing and event identification:

Imaging and pulse artifact were removed offline and IEDs coded as described in Chapter 3.

Following this seizures were identified and divided into up to 3 phases each defined by an onset time and duration as follows:

- Early ictal phase, defined as the earliest observable change on EEG. This phase was not identified in patients in whom clinical features evolved simultaneously or in advance of EEG change.
- Clinical ictal phase, defined as the onset of myogenic artifact and/or clinical manifestation of the seizure.
- Late ictal phase, defined by onset of high amplitude low frequency change following the seizure onset on EEG.

Three distinct phases were identified in 5/9 patients (#1, 3, 4, 5, 9) and two phases in two patients (# 6, 7). A single phase was identifiable in patient 2. In patient 8 the seizure could not be modeled from the EEG as the clinical events had no EEG correlate (Table 3.1 gives details of the seizures recorded, and details of the phases used to model the BOLD signal can be found in Table 3.2).

7.3.3 fMRI pre-processing:

fMRI time series were preprocessed as described in Chapter 2. No dataset was discarded regardless of the amount of head movement.

To characterize head movements for each dataset, inter-scan motion data derived from the SPM scan-realignment process were summarised as the minimum, maximum,
average inter-scan displacement and the number of events in which head movement exceeded 1 mm (see )

7.3.4 General Linear Model Analysis

We sought to identify patterns of BOLD change associated with each of the (up to) three ictal phases: pre-ictal EEG changes, ictal EEG changes and post-ictal EEG changes. In cases with repeated stereotyped seizures, the model was designed to estimate BOLD effects that were consistent across seizures. We also sought to use a flexible model to allow for deviation from the canonical HRF.

Therefore two EEG-based modeling approaches were used:

1. Canonical HRF

For each seizure type, up to three phases (described above) were included in the model as separate conditions to identify patterns of BOLD change associated with each phase. Each phase was represented by a block from onset to offset and convolved with the canonical haemodynamic response function and its temporal and dispersion derivatives, resulting in a total of three separate regressors for each phase. In addition, BOLD signal changes associated with IEDs were modeled. Two F contrasts were specified to assess significant BOLD changes:

- Across all phases, allowing comparison with the results of Fourier basis set analysis.
- Specific to each phase.

Effects were considered significant at a threshold of \( p = 0.05 \) (Family-wise Error (FWE) correction for multiple comparisons). The direction of the BOLD
changes for any given cluster was determined by plotting the fitted response at
the voxel with maximal t-score within the cluster and observing the event-
related BOLD response.

2. Fourier Basis Set

In those cases (#1, 3, 4, 7 and 9) in whom seizures were long enough (longer than
3TR = 9 s), we attempted to model inter-regional variations in the temporal
evolution of the BOLD signal during the seizure, using a model capable of capturing
signal changes of arbitrary shape arising consistently across events.

We used a Fourier basis set over a time window corresponding to the longest
period common to all seizures within a patient. The number of Fourier basis
functions was chosen according to the event duration so that the model's temporal
resolution was constant across cases and events, determined by the term with the
shortest wavelength which was set at 2TR (6 s). Events that could not be modeled
using Fourier regressors, for example those in which seizure length varied (see
case 3), were included in the model using the canonical HRF approach (above).

A F contrast was used to assess ictal BOLD changes corresponding to any linear
combination of the Fourier basis set functions, considered significant at p < 0.05
(FWE)
resulting in an $\text{SPM}(F)$ map, which was compared with that obtained for the canonical HRF model.

For both the Canonical HRF and Fourier Basis Set approaches, the estimated time courses of event-related BOLD signal change were plotted for the most significant cluster and the cluster nearest to the seizure onset zone.

7.3.5 Classification of independent components

After decomposition, automatic IC classification was applied (De Martino, Gentile et al. 2007) resulting in sorting the IC among the following types: (1) the ‘BOLD’ class, which included components that are thought to consistently reflect task-related, transiently task-related and brain state-related (e.g. default state) neuronal activity; (2) residual motion artefacts; (3) EPI-susceptibility artefacts; (4) physiological noise; (5) noise at high spatial frequency; and (6) noise at temporal high frequency.

The classifier previously applied in interictal data (Rodionov, De Martino et al. 2007) has been trained using a dataset from healthy volunteer and is designed to be inclusive rather than restrictive with respect to BOLD components in order to reduce the probability of misclassification of a BOLD-related IC. The ability of the classifier to reveal BOLD components means it can separate stereotypical components of normal brain activity such as the so-called ‘default mode’ network (Raichle, MacLeod et al. 2001) and components related to auditory and sensory stimulation which are observed during rest.

The BOLD components were further classified into the following sub-types by visual inspection by an observer (RR)*, blinded to the clinical data, which enabled objective

* RR = Dr Roman Rodionov, colleague at the Epilepsy Society MRI Unit
reduction of the classified components. In addition, the components classified as EPI low-frequency drift artefact were also inspected as these may correspond to BOLD ictal activity. This classification resulted in three IC sub-types:


2. Misclassified: likely to reflect artefacts.

3. Potentially epileptic BOLD IC: have appearance of BOLD signal changes linked to neuronal activity.

ICs belonging to the “potentially epileptic” sub-type were reviewed (myself) to identify ictal components, based on their spatial relationship to the epileptogenic zone as defined by all available investigations. In cases when no ictal IC were found in the “potentially epileptic” sub-type (themselves a sub-set of the BOLD or EPI classes), ICs in the other classes (motion, noise) were reviewed to identify ictal ICs. The IC time-course represents activity contributing to each voxel with weighting coefficient determined by the map of the IC. Given that the resulting ICs represent independent sources the time-courses represent activity of the independent sources and confounds even though the spatial variant of ICA is applied. Assuming that the confounding effects were separated in the form of confounding ICs, we visually evaluated the temporal correspondence of the time course of the ictal ICs in relation to the scalp EEG (myself).

7.3.6 Comparison of the GLM results with intracranial data

In case 3, comparison was only possible with non-invasive data as the icEEG was abandoned.
In the other cases, patient-specific T1-weighted MRI scans were co-registered and fused with a post-operative CT with the sub-dural grid or depth electrodes in situ (Engel, 2001). These fused images were co-registered with the SPM(F) to identify regions of BOLD signal change in relation to the intracranial EEG. The degree of concordance of the GLM results was assessed based on the entire statistical maps: these were classified as follows:

- **Concordant (C)**, when all significant BOLD clusters were concordant with the site of seizure onset identified on intracranial EEG, provided that the area of maximal signal change was in the same gyrus and within 2 cm of the intracranial EEG electrode marking seizure onset, allowing for inaccuracies of co-registration and intra-operative brain shift (Nimsky et al., 2000)

- **Concordant plus (C+)** when the BOLD cluster containing the global statistical maximum was concordant but additional, discordant clusters were revealed

- **Discordant (D)**, when no cluster was concordant.

- **NULL**, when no significant activation was revealed (Table 4).

### 7.3.7 Independent component analysis (ICA)

Spatial ICA (Formisano, Esposito et al. 2004) (McKeown, Hansen et al. 2003) (McKeown, Makeig et al. 1998) as implemented in Brain Voyager QX software (Brain Innovation, Maastricht, Netherlands) was performed on fMRI data to reveal BOLD patterns specific to the seizure onset zone and to study the time course of the BOLD signal change.

The mathematical details of the ICA for fMRI are described elsewhere (McKeown, Makeig et al. 1998, McKeown, Hansen et al. 2003). Details of implementation of ICA in BrainVoyager QX can be found in (Formisano, Esposito et al. 2004). Inclusive masks
of the grey matter covering the neocortex and main sub-cortical structures were created by applying brain tissue segmentation (SPM5, www.fil.ion.ucl.ac.uk/spm) to T1-weighted images. The resulting masks were then affine transformed to Talairach space using Brain Voyager QX as well as the realigned fMRI images.

In summary, the technique constrains the analysis to grey matter and uses a fixed point ICA algorithm to separate signals generated by different sources. The ICA decomposition can be expressed as:

\[ X = AS \]

where \( X \) is the measured fMRI signal, \( S \) the spatial maps of the decomposition and \( A \), the time courses defining the relative weighting of the spatial maps throughout the experiment. We estimated \( A \) and \( S \), using the hierarchical (deflation) mode of the FastICA algorithm (Hyvärinen, 1999), after reduction of the temporal dimension of the data set with principal component analysis to 80 dimensions. This number of dimensions was selected following a demonstration that this number was stable in previous work (Rodionov, De Martino et al. 2007).

The ICs were overlaid on the patient specific T1-weighted image in Talairach space which is implemented as part of the ICA in Brain Voyager QX.

ICs were overlaid on the patient specific T1-weighted image in Talairach space and anatomically labelled.

### 7.3.7.1 Classification of independent components

Automatic IC classification sorted the components into (De Martino, Gentile et al. 2007): (1) ‘BOLD’, including components which reflect normal physiological resting and
task related brain states (Mantini et al., 2007, Raichle et al., 2001 and Schmithorst & Brown, 2004); (2) EPI-susceptibility artifacts; (3) motion artifacts; (4) physiological noise; (5) noise at high spatial frequency; and (6) noise at temporal high frequency. We observed motion highly correlated with seizures in two patients (4 and 7), resulting in components with features of > 1 of the above types, and undertook a further decomposition into 160 components to attempt to separate these components.

The classifier (Rodionov, De Martino et al. 2007) and (De Martino, Gentile et al. 2007) was trained using a dataset from a healthy volunteer and designed to be inclusive with respect to BOLD components to reduce the probability of misclassification of a BOLD-related IC. Components classified as BOLD or EPI low-frequency drift artifact was inspected by an observer blinded to the clinical data, and divided into. Three further subtypes according to their spatial pattern as follows:

1. Misclassified as BOLD (i.e. the spatial and temporal pattern suggested that the component should have been classified as noise).
3. ‘Potentially epileptic’ (those exhibiting BOLD features, which do not fit 1 or 2).

7.3.7.2 Identification of ictal components

The fused images showing the intracranial electrodes were transformed to Talairach Space and the ‘potentially epileptic’ components identified using ICA were overlaid and reviewed to identify ‘ictal components’, based on their spatial relationship to the seizure onset zone defined on icEEG. When no ictal IC was identified among these, ICs in the
other classes (motion, noise) were reviewed (potential ictal ‘non-BOLD’ ICs) owing to
the fact that the classifier has not previously been tested in patients with epilepsy.

7.3.8 Correlation of GLM with IC time courses

The EEG time course (as input to the GLM) was compared with the signal time course
of ‘ictal components’ by calculating the correlation coefficient between the EEG time
course extracted from the fMRI model following convolution with the canonical HRF
and the respective ictal IC time course. The correlation between both the ‘early ictal’
phase and the ‘total model’ across all phases (the most closely related to the seizure
onset zone), and a representative ictal IC for each case.

7.4 Results

Of the 101 patients who underwent EEG-fMRI, focal seizures were recorded in nine, of
which four had frontal lobe epilepsy, two had temporal lobe epilepsy, one had parietal
lobe epilepsy and the remaining two were less well localized. Between 1 and 5
seizures per patient were recorded during EEG-fMRI. Clinical seizures were recorded
in 8/9 patients; the other patient had 3 electrographic seizures. The clinical data are
summarized in Table 7.1.
<table>
<thead>
<tr>
<th>Type</th>
<th>Semiology</th>
<th>IEDs in scanner</th>
<th>Ictal EEG</th>
<th>MRI</th>
<th>icEEG</th>
<th>Head motion &gt;1mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1LFLE</td>
<td>R foot parasthesia, R hand and foot jerks</td>
<td>Bilat sharp theta</td>
<td>1 event (50 secs): bi-frontal sharp waves, rhythmic theta</td>
<td>FCD, LsupF gyrus</td>
<td>SOZ= IZ: L sup F gyrus</td>
<td>-</td>
</tr>
<tr>
<td>2RFLE</td>
<td>L head and eye deviation, grunt, LOC</td>
<td>RF spime wave</td>
<td>Rhythmic bifrontal spike-wave max F4-C4</td>
<td>R F atrophy</td>
<td>SOZ=IZ:R orbF/pre-F córtex, R lat premotor</td>
<td>2/1.44/1.5/1.58</td>
</tr>
<tr>
<td>3LFLE:</td>
<td>Loss of awareness, R upper limb jerking</td>
<td>L and RF sharp waves</td>
<td>5 events (21, 32, 21, 25, 59 secs): Beta/gamma activity, LF (max F3), rhythmic bilateral slowing</td>
<td>L frontal gliosis</td>
<td>N/A</td>
<td>15/1.0/2.9/6.1</td>
</tr>
<tr>
<td>4RFLE:</td>
<td>L sided jerks, face and arm</td>
<td>RF theta</td>
<td>4 events (111, 163, 147, 165 secs): R F delta, rapid bilateral spread (max F4-P4).</td>
<td>R FT lesion: R Inf-F and Sup-T gyril</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5RPLE</td>
<td>L foot sensory disturbance, L head version, vocalization</td>
<td>RF slowing (max F4)</td>
<td>2 events (28, 19 secs): 30 Hz activity at F4-C4, rhythmic max at F4-C4</td>
<td>Normal</td>
<td>SOZ= IZ: R post-central gyrus</td>
<td>7/1.1/2.6/8.0</td>
</tr>
<tr>
<td>6RTPLE</td>
<td>Blinking, rapid loss of awareness, vocalization</td>
<td>RP spikes and polyspikes</td>
<td>3 events (15, 12, 66 secs): RP beta, bilateral rhythmic discharge</td>
<td>FCD base R T, PO lobes</td>
<td>SOZ: R Inf Tand P lobes</td>
<td>-</td>
</tr>
<tr>
<td>7ROLE</td>
<td>Visual hallucination, blinks, automatisms</td>
<td>LT spikes bilateral post theta.</td>
<td>1 event (87 secs): Blink artifact rhythmic bilateral delta</td>
<td>FCD R P and O lobes</td>
<td>SOZ: R O lobe</td>
<td>-</td>
</tr>
<tr>
<td>8RFLE</td>
<td>L foot and arm clonic jerks</td>
<td>R F spikes</td>
<td>Multiple clinical ictal events not related to EEG</td>
<td>Normal</td>
<td>SOZ: R medial F and P</td>
<td>3/1.7/3.9/5.6</td>
</tr>
<tr>
<td>9L TLE</td>
<td>Manual automatism</td>
<td>None</td>
<td>1 event (33 secs): Fast activity: L then RT, LT atrophy</td>
<td>SOZ: L mesial T and T pole</td>
<td>5/1.0/1.5/2.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: R = right, L = left, IZ = irritative zone, SOZ= seizure onset zonezone, T = Temporal, F = Frontal, O= Occipital, P = Parietal, orbF = fronto-orbital, lat = lateral, Inf = inferior, LOC = loss of consciousness, TLE = temporal lobe epilepsy, PLE = parietal lobe epilepsy, FLE = frontal lobe epilepsy Inf= inferior, Sup = superior, EEG= electroencephalogram, FCD= focal cortical dysplasia,. The ictal event durations are the sum of durations of early, clinical and late ictal phases.
7.4.1 General Linear Model

Table 7.2 summarises the results of the canonical and Fourier basis set GLM analyses. Case reports are presented below.

7.4.1.1 Canonical HRF

Significant BOLD signal changes were found in 7/9 cases using the canonical GLM. In 4 cases (cases #1, 2, 3, 5), BOLD localization across all ictal phases was concordant with the seizure onset zone. In 5 cases (#1, 3, 4, 5, 7), there were significant BOLD changes linked to the early ictal EEG phase, which were concordant in 3 cases (#3-5). In 5/7 cases (#1, 3, 4, 5, 6), there were significant BOLD signal changes linked to the clinical phase of the seizure, concordant with seizure onset zone in two of these (#3 and 5). In 4/7 cases (#1, 3, 4, 5) significant BOLD changes were observed in relation to the late ictal phase, one of which (#5) was concordant with the seizure onset zone. In two cases (#1 and 3), BOLD localization was discordant for one or all individual phases but concordant when all phases were considered together. In case #8, the ictal events could not be modeled in a GLM as the patient’s seizures did not correlate with EEG change.

7.4.1.2 Fourier Basis Set

The Fourier basis set analysis showed significant BOLD signal changes in 3 of the 5 cases analysed (#1, 3 and 7); and the degree of concordance was the same as for the canonical HRF analysis. In case 1, the global maximum was concordant with the seizure onset zone. In case #3, the most significant BOLD cluster was remote from the seizure onset but a smaller and less significant cluster was concordant with the
structural lesion and presumed seizure onset. In case #7, the results were discordant. The temporal pattern of the BOLD signal revealed by the Fourier analysis varied between regions by shape and temporal delay of the high amplitude responses.

### 7.4.1.3 Independent Component Analysis

Table 7.3 summarizes the ICA results.

The mean numbers of IC classified as BOLD and EPI per 20 min EEG-fMRI run were 7 (range 3-14) and 24 (range 14-36) respectively. Over both runs a mean of 6 ICs were characteristic of normal physiological activity (Beckmann and Smith, 2004; Laufs et al., 2003) and a mean of 4 BOLD IC per data set identified as „potential epileptic components“.

Between 1 and 2 ICs spatially concordant with the seizure onset zone and classified as BOLD or EPI were observed in 5/9 cases (1,2,3,5 and 9). An IC spatially concordant with the seizure onset zone and classified as mixed BOLD/motion was observed in 1 case. In the remaining cases, at least one IC not classified as BOLD or EPI were observed spatially concordant with the seizure onset zone. In 8/9 cases, localisation was confirmed on intracranial data.

### 7.4.1.4 Correlation of GLM and IC time courses

In 5 cases (#1, 2, 3, 5 and 7), the early ictal phase and/or total model (i.e. the \{SPM-F\} across all phases) was significantly (p<0.001) correlated with identified “ictal” or “potentially ictal non-BOLD” components. The GLM model was most highly (r >0.2, p<0.001) correlated in cases #1, 3 and 5. In the remaining cases no phase of the EEG time course was significantly correlated with any ictal component. The “late phase” and
“clinical phase” of the EEG were not significantly correlated with any ictal component in all but one (case #5) cases (see table 7.4).
Table 7.2 Results of General Linear Model Analysis of ictal data

<table>
<thead>
<tr>
<th>Ictal phases used for modelling</th>
<th>Ictal canonical GLM</th>
<th>Clinical ictal EEG</th>
<th>Late ictal EEG</th>
<th>All phases combined</th>
<th>Ictal Fourier basis set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early ictal EEG</td>
<td>Clinical ictal EEG</td>
<td>Late ictal EEG</td>
<td>All phases combined</td>
<td>Ictal Fourier basis set</td>
</tr>
<tr>
<td>1 Early/clinical/late</td>
<td>R F Orb.(+)</td>
<td>R F Orb.(+)</td>
<td>L mid-T.(-)</td>
<td>L sup F gyrus (+)</td>
<td>L sup F gyrus, L and R inf T</td>
</tr>
<tr>
<td>2 Complete events</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3 Early/clinical/late</td>
<td>L sup F gyrus,(+)</td>
<td>L middle F gyrus,(-)</td>
<td>L Occ, Biphasic (neg-pos)</td>
<td>L sup F gyrus; L post T (-)</td>
<td>L inf F gyrus and L Par</td>
</tr>
<tr>
<td>4 Early/clinical/late</td>
<td>R Occ; bil mesial F triphasic (+/-/+)</td>
<td>Bil mesial and lat F,(+)</td>
<td>R pre-central gyrus,(+)</td>
<td>R pre-central gyrus, 3-phasic (+/-/+)</td>
<td>NULL</td>
</tr>
<tr>
<td>5 Early/clinical/late</td>
<td>Widespread (+)</td>
<td>Widespread (-)</td>
<td>Widespread (+)</td>
<td>Widespread (+)</td>
<td>N/A</td>
</tr>
<tr>
<td>6 Early/clinical/late</td>
<td>N/A</td>
<td>R mesial pre-F cortex (+)</td>
<td>NULL</td>
<td>R mesial pre-F cortex, (+)</td>
<td>N/A</td>
</tr>
<tr>
<td>7 Early/clinical/late</td>
<td>Bil Occ; L more significant,bi-phasic (-/+)</td>
<td>NULL</td>
<td>N/A</td>
<td>Bil Occ; L more significant, bi-phasic (-/+)</td>
<td>Rt temp; L Occ</td>
</tr>
<tr>
<td>8 Not modelled</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9 Early / clinical /late</td>
<td>NULL</td>
<td>NULL</td>
<td>NULL</td>
<td>NULL</td>
<td>NULL</td>
</tr>
</tbody>
</table>

Abbreviations: R= right, L = left, F= frontal, T = temporal, P= parietal, Occ = occipital, bil= bilateral, inf= inferior, sup= superior, orb= orbital (-) = first deflection in the haemodynamic response is negative, (+) = first deflection in the haemodynamic response is positive NULL= no BOLD response recorded.
Table 7.3 Results of Independent Component Analysis

<table>
<thead>
<tr>
<th>No</th>
<th>Number of BOLD IC</th>
<th>Number of EPI IC</th>
<th>Number and classification of ictal IC</th>
<th>Concordance with icEEG?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>25</td>
<td>1: BOLD</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>36</td>
<td>2: BOLD</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>20</td>
<td>1: motion</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>15</td>
<td>1: BOLD + motion</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>14</td>
<td>2: BOLD</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>33</td>
<td>1: SDN</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>36</td>
<td>1: EPI</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>22</td>
<td>1: BOLD</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>17</td>
<td>1: thFN</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 7.4 Concordance of ictal EEG-fMRI and icEEG

<table>
<thead>
<tr>
<th>Case (events)</th>
<th>Canonical GLM</th>
<th>Fourier GLM</th>
<th>ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire</td>
<td>Early</td>
<td>Clinical</td>
</tr>
<tr>
<td>1 (1)</td>
<td>C+</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>2 (20)</td>
<td>C+</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3 (5)</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>4 (4)</td>
<td>C</td>
<td>D(*)</td>
<td>D</td>
</tr>
<tr>
<td>5 (2)</td>
<td>C+</td>
<td>C+</td>
<td>C+</td>
</tr>
<tr>
<td>6 (3)</td>
<td>D</td>
<td>n/a</td>
<td>D</td>
</tr>
<tr>
<td>7 (1)</td>
<td>D*</td>
<td>D*</td>
<td>NULL</td>
</tr>
<tr>
<td>8 (**)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9 (1)</td>
<td>NULL</td>
<td>NULL</td>
<td>NULL</td>
</tr>
</tbody>
</table>

Abbreviations: BOLD = blood oxygen level dependent signal, EPI = echo planar imagin, IC = indpendet component, GLM = general linear model, C = Concordant, D = discordant (for definitions of concordance, please see main text section 7.3.6)
Table 7.5 Correlation of fMRI GLM with time course of the respective ‘ictal’ independent component

<table>
<thead>
<tr>
<th>Case</th>
<th>Early ictal phase</th>
<th>Total model (all phases combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>1</td>
<td>0.170</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>−0.474</td>
<td>0.000</td>
</tr>
<tr>
<td>4</td>
<td>−0.009</td>
<td>0.857</td>
</tr>
<tr>
<td>5</td>
<td>−0.123</td>
<td>0.014</td>
</tr>
<tr>
<td>6</td>
<td>−0.029</td>
<td>0.435</td>
</tr>
<tr>
<td>7</td>
<td>0.148</td>
<td>0.005</td>
</tr>
<tr>
<td>8</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>−0.044</td>
<td>0.563</td>
</tr>
</tbody>
</table>

R = correlation coefficient. P = probability. Figures are rounded to nearest 0.001. n/a = not applicable, where the stated model did not apply to this dataset (see main text).

7.4.2 Case Reports

Case 1 (Figure 7-1)

Left frontal lobe Epilepsy. A 20 year-old female with left superior frontal gyrus focal cortical dysplasia. A single simple motor seizure was recorded during EEG-fMRI lasting 48s. Ictal EEG consisted of rhythmic theta in fronto-temporal leads bilaterally (early ictal phase), a clinical ictal phase, followed by high amplitude sharp waves of the same distribution (late ictal phase). Interictal runs of sharp theta were also recorded during scanning.

Ictal onset zone: left superior frontal gyrus confirmed by intracranial EEG;
Canonical GLM analysis: the F contrast across all phases revealed significant BOLD changes in the left superior frontal gyrus, left and right inferior temporal border, with global maximum in the ictal onset zone (see figure). BOLD signal changes related to each separate ictal phase seen on the SPM(F) generated for each phase separately were remote from the ictal onset zone.

Fourier set GLM analysis: The entire seizure was modelled. The seizure-related BOLD pattern was similar to the Canonical GLM result (contrast across all phases) but much more extensive. The time course for the cluster containing the global statistical maximum reached amplitude maximum 11s into the event which was 5 s after the beginning of the clinical ictal phase. The second of the two most significant clusters showed signal which reached minimum of the negative BOLD signal change at the end of the clinical ictal phase and the beginning of the post-ictal phase (Figure 7-1 b).

ICA: one BOLD IC was classified as ictal, with the largest cluster concordant with the ictal onset zone and additional, smaller clusters in the ipsilateral temporal lobe and contra-lateral frontal lobe. The time course of the IC showed 3 high amplitude transients each lasting 9-15 s: 15 s prior to and at the start of the ictal EEG change respectively and 6 minutes post ictal onset.
Figure 7-1 Patient 1, ictal series

a. Seizure related BOLD signal change modeled with canonical HRF in the left primary motor cortex overlying T1 weighted MRI (all 3 phases), p<0.05 FWE corrected. b. Seizure related BOLD signal change modeled with Fourier basis set overlying T1-weighted MRI fused with CT with intracranial electrodes in situ (p<0.05), FWE corrected. c. Same as a overlying a 3 d rendered image showing position relative to intracranial electrodes (green = SOZ, red = IZ). d. Time course of the BOLD signal change over the course of the seizure (red, blue and green boxes delineate early, clinical and late ictal phases respectively). The time course for the cluster containing the global maximum reached maximal amplitude 11 s after electrographic onset (5 s after clinical onset). e. Results of
ICA overlaid on T1-weighted MRI fused with a CT containing sub-dural electrodes: one BOLD IC was classified as ictal, with the largest cluster concordant with the seizure onset zone and additional, smaller clusters in the ipsilateral temporal lobe and contra-lateral frontal lobe.

Results of ICA overlaid on 3d-rendered T1-weighted MRI fused with CT with intracranial electrodes in situ. Timecourse of independent component in e and f (note slow rhythmic fluctuations before seizure onset).

Case 2

Right frontal lobe epilepsy. A 24 year-old male with right frontal cortical atrophy. Ictal EEG activity consisted of continuous bilateral frontal rhythmic spike-wave discharges with infrequent intervals of 2 s or less, and therefore could not be represented as blocks. Individual discharges were used as a basis for the GLM by representing each as a discrete delta function.

Ictal onset zone: right medial orbiot/prefrontal, confirmed by intracranial EEG;

GLM analysis using canonical HRF: BOLD signal changes correlated with individual spike-wave discharges were maximal in right premotor cortex and SMA with additional clusters concordant with the seizure onset zone.

ICA: two BOLD-classified IC were observed spatially concordant with the ictal onset zone with clusters in the right anterior cingulate and right orbi-to-frontal cortex. Slower frequency and higher amplitude of the BOLD signal was seen for the epochs prior to the ictal events.

Case 3

Left frontal lobe epilepsy. A 37 year-old male with post traumatic gliosis in the left frontal lobe. A cluster of five brief motor seizures coinciding with head turning and
coughing were recorded during the second run of EPI. Ictal EEG change consisted of a bi-frontal slow complex followed by muscle artefact, rhythmic activity on the left and then widespread theta. All three ictal phases were revealed in the ictal EEG with the following typical activity: early ictal phase consisting of bi-frontal theta maximal in F3, clinical ictal phase obscured by muscle artefact and post-ictal phase showing widespread high amplitude rhythmic theta.

Ictal onset zone: presumed to be in the left middle frontal gyrus; intracranial EEG recording was not performed in this case.

GLM analysis using canonical HRF: BOLD signal changes correlated with the three combined ictal phases, and early and clinical ictal phases individually, were concordant with the ictal onset zone. Early ictal phase-correlated BOLD with maximum in the left superior and middle frontal gyri, just anterior to motor cortex. Clinical ictal phase-correlated BOLD signal change was concordant with the structural lesion in the left frontal lobe.

GLM analysis using a Fourier basis set: 18-second blocks from the start of the late ictal phase were modelled using a Fourier basis set with the variable duration early and clinical phases modelled using the canonical HRF. Multiple clusters were observed related to the late ictal phase with the cluster containing the global maximum involving the left temporal lobe and post-central gyrus plus cluster in the left superior and middle frontal gyri, just anterior to motor cortex. The fitted BOLD time course for those two clusters showed similar patterns with large bi-phasic changes at around 0-9s (time course for one cluster being mirror image of the other in this period) and 30-40s post event onset.
ICA: none of the ICs classified as BOLD or EPI by the automatic classifier was spatially concordant with ictal onset zone. Two ICs classified as motion-related were identified within the left frontal lobe.

**Case 4**

Right frontal lobe epilepsy. An 18 year-old male with an MRI abnormality in the right fronto-temporal region thought to indicate an infarct. Four simple motor seizures consisting of left facial twitching lasting 111, 163, 147, 165 seconds respectively were recorded during EEG-fMRI). All three ictal phases were observed on the ictal EEG: rhythmic theta in F4-P4 (early ictal); spread of the theta to all right sided leads followed by muscle artefact (clinical ictal phase) and finally high amplitude delta across all leads (late ictal phase).

**Ictal onset zone:** right frontal cortex close to the motor cortex confirmed by intracranial EEG.

**GLM analysis using canonical HRF:** BOLD signal changes correlated with the three combined ictal phases and the late ictal phase were concordant with the ictal onset zone. Early ictal-correlated BOLD signal changes were only significant at $p<0.001$, uncorrected for multiple comparisons with a maximum located in the right pre-central gyrus.

**GLM analysis using Fourier basis set:** Due to varying duration of seizures, the first 36s of the early ictal phase was modelled as one Fourier block and the remainder of the seizure as a separate Fourier block. No significant BOLD signal change was revealed.

**ICA:** IC spatially concordant with the ictal onset zone and classified as mixture of BOLD and motion related artefact was observed after application of ICA with doubled number
of IC. High amplitude signal change was observed at the end of each ictal event (see time course of the IC).

The initial ICA decomposition with 80 IC contained a motion classified IC which contained small and weak (low z score) clusters in the location revealed by icEEG.

The time-courses of these two ICs contained correlated slow oscillations of high amplitude. It was possible to separate this component by means of a secondary decomposition into 160 components.

**Case 5**

Right parietal lobe epilepsy. A 19 year-old female with right post-central gyrus focal cortical dysplasia. Two seizures were recorded during EEG-fMRI consisting of brief loss of awareness and clonic movement of the left hand and arm. Ictal EEG showed fast activity in the right para-central leads (max Fz-Cz) (early ictal phase), followed by synchronised slowing across all leads (clinical phase). This activity ceased abruptly with no evident post ictal change. No IED were recorded.

*Ictal onset zone:* Intracranial EEG revealed a seizure onset zone which included the lesion (right post central gyrus) and tissue adjacent to it.

**GLM analysis using canonical HRF:** BOLD signal changes correlated with each phase separately and all phases together were widespread in all lobes. The global maximum on the SPM(F) showing BOLD signal correlated with early ictal phase was co-located with the ictal onset zone.

**GLM analysis using a Fourier basis set** was not carried out as the two recorded seizures had different durations (28 and 19 sec).
ICA: An IC was located in the right post central gyrus extending laterally spatially concordant with presumed ictal onset zone. This IC was reproducible in both recording sessions showing very similar spatial maps. This IC was classified as BOLD for the first session and as EPI for the second session. Haemodynamic changes time-locked to ictal EEG were observed on time course of the ICs.

Case 6

Right posterior epilepsy. A 27 year-old male with extensive right hemisphere focal cortical dysplasia. Interictal right temporal poly-spikes and right parietal spike wave were recorded during EEG-fMRI. Three seizures (duration: 15, 12 and 66 s) were recorded (Figure 7-2). The EEG was divided into two phases: clinical phase: right sided widespread sharp waves with some EMG artefact and late ictal phase consisting of rhythmic delta across all leads, maximal on the right.

Ictal onset zone: right posterior temporal and parietal lobes, with a widespread irritative zone, confirmed by intracranial EEG.

GLM analysis using canonical HRF: BOLD signal changes related to clinical ictal phase and combined clinical and late ictal phases maximal in the right frontal lobe.

(GLM analysis using a Fourier basis set was not carried out as the seizures were too short in duration).

ICA: a single IC concordant with the ictal onset zone was classified as spatially distributed noise.
Figure 7-2: Case 6, ictal series.

A. Results of canonical HRF overlaid on T1 weighted MRI. BOLD signal changes related to clinical ictal and 'all ictal' phases were maximal in the right frontal lobe, remote from the seizure onset zone. SPM(F) p<0.05 FWE corrected for multiple comparisons. B. Results of ICA: a single IC concordant with the ictal onset zone classified as spatially distributed noise overlaid on T1 weighted MRI fused with CT with ic electrodes in situ. Green shaded area indicates position of seizure onset zone. C. Results of ICA overlaid on a surface rendering of the T1 weighted MRI illustrating the position of the intracranial electrodes. Green dashed lines illustrate those electrodes recording seizure onset. D. Time course of the IC shown in B and C.
Case 7

Right posterior epilepsy. A 24 year-old female with previously operated right medialparieto-occipital dysembryonic neuroendothelial tumour (DNET). No IED were recorded during EEG-fMRI. A single seizure was recorded. The patient experienced elemental hallucination of lights followed by confusion and urinary incontinence. The early ictal EEG change consisted of widespread slowing (early ictal phase) followed by motion artefact (clinical ictal phase). No late ictal phase could be identified on EEG.

Ictal onset zone: right medial occipital cortex; concordant with irritative zone and consistent with findings of intracranial EEG. She experienced a 50% seizure reduction following right occipital resection limited by the proximity of primary visual cortex.

GLM analysis using canonical HRF: The most significant cluster across early and clinical ictal phases was located in the right occipital lobe. No significant change was revealed for the clinical ictal phase. A less significant and smaller cluster of BOLD signal change correlated across early and clinical ictal changes on EEG was concordant with the ictal onset zone.

Fourier set GLM analysis: The most significant cluster of BOLD change related to the whole seizure was in the right temporal lobe. The most extensive cluster was similar to that revealed by the canonical GLM model. A less significant and smaller cluster of BOLD signal change was concordant with the ictal onset zone. Examination of the time course in the two most significant clusters revealed large BOLD signal changes confined to the clinical ictal phase.

ICA: Both the ICA decomposition with 80 IC and with 160 IC revealed a motion classified IC spatially concordant with ictal onset zone. The time-course of that IC
contained high frequency activity which is not relevant for BOLD signal changes and confirms the confounding character of this IC. An IC classified as related to EPI-susceptibility artefact (an EPI IC further) was revealed after ICA decomposition with 160 IC in the right occipital lobe spatially concordant with ictal onset zone.

**Case 8**

Right medial frontal epilepsy. A 19 year-old male with normal MRI. Right frontal, midline and right parietal spike wave and sharp wave complexes were recorded during EEG-fMRI. In addition, multiple episodes of left leg jerking were observed on video during the EEG-fMRI acquisition. Ictal EEG consisted of periods of right-frontal slowing, clusters of spike-wave discharge or normal background and was not used as a basis for BOLD modelling as ictal events could not be clearly defined on the scalp EEG.

*Ictal onset zone*: right medial frontal and parietal cortex, confirmed by intracranial EEG.

*GLM analysis using canonical HRF*: IED-related BOLD clusters in the right medial frontal and right parietal regions were concordant with ictal onset zone.

*GLM analysis using a Fourier basis set* was not performed due to lack of clear ictal EEG changes.

*ICA*: an IC classified as BOLD and presenting an extensive right medial frontal cluster was concordant with the ictal onset zone.
Case 9

Left temporal lobe epilepsy. A 42 year-old male with left hippocampal sclerosis. Left temporal spikes were recorded during EEG-fMRI. A single seizure was recorded during scanning with the EEG showing fast activity across both temporal regions (early ictal phase), followed by myogenic artefact (clinical ictal phase) and then simultaneous synchronized slow waves across both hemispheres (late ictal phase).

Ictal onset zone: left mesial temporal structures (hippocampus, amygdala) and left temporal pole; widespread irritative zone, confirmed by intracranial EEG.

GLM analysis using canonical HRF: No significant BOLD signal change associated with the ictal phases or interictal events was revealed.

Fourier set GLM analysis: No significant BOLD signal change was revealed in the brain.

ICA: a single IC classified as high-frequency temporal noise and located in the left anterior temporal lobe was concordant with the ictal onset zone. IC time course demonstrated a good degree of temporal correspondence with the recorded seizure.
7.5 Discussion

7.5.1 Summary of findings

This experiment was aimed at identifying haemodynamic patterns specifically linked to ictal events or to the ictal onset zone and to improve methodology for the analysis of ictal events in EEG-fMRI data. Three different methods of ictal EEG-fMRI data analysis (two model-based strategies with fixed and flexible model of HRF and one data-driven approach) were applied on data acquired in 9 patients who had focal seizures during scanning. The spatial concordance of the results and localization of the ictal onset zone differed between the three methods. Despite methodological complications related to uncertainty about expected haemodynamic response and contamination of the fMRI data by motion, a good degree of concordance was observed particularly when a degree of flexibility in relation to assumptions about the ictal BOLD signal was allowed. The degree of concordance was less than that reported by previous studies, (Tyvaert, Hawco et al. 2008, Donaire, Bargallo et al. 2009).

The use of an exploratory approach to the analysis of ictal fMRI data allowed the identification of a wide range of BOLD patterns exhibiting temporal correlation with ictal events and spatial correlation with the region of ictal onset. Although the yield of EEG-based modelling was high and the majority of the maps across whole seizures were found to be concordant with the ictal onset zone, the results of analysis of individual EEG based phases as well as that using a Fourier basis set highlights the hazards of using scalp EEG based models.

The effect of motion on the results could be gleaned from the relationship between quantitative indicators of the degree and nature of motion and the presence or absence
of concordant BOLD patterns, but the number of cases limits our ability to draw any statistically valid conclusions regarding this.

In most cases with multiple seizures, significant BOLD changes were revealed lending validity to the modelling approach.

The successful identification of spatially concordant independent components in the fMRI data without reference to the EEG from a small subset of candidate components of the initial 80 ICs, in a large proportion of the cases is encouraging. The complex dynamics of the observed components are not unexpected given complexity and non-stationary dynamics of the ictal neurophysiology, and provide another illustration of the challenges faced by EEG-based modelling.

In two cases, BOLD time courses derived from the Fourier analysis had non-zero values at event onset, suggesting pre-ictal BOLD changes. The ICA analysis proposed in this work was partly an attempt to address these issues. In its current implementation in the SPM software, the Fourier modelling approach is limited to fixed-duration modelling blocks. This, combined with my wish to map BOLD patterns that are consistent across events (when multiple seizures were captured) has constrained the approach to modelling the longest ictal epoch which is common to all events but always starting at the onset of any given phase, which may be reasonable given the intrinsic interest in what happens in the initial moments of an event rather than post ictal haemodynamic changes.

I was able to demonstrate statistically significant correlation between the time courses of spatially independent 'ictal components' with the time course of seizures as recorded on scalp EEG in those cases where the seizure onset was easily defined on scalp EEG (cases 1, 3, 5 and 7).
In this experiment I avoided comparing results of GLM and ICA owing to the possibility that the detected ictal ICs represent ictal activity, which is not described by the two GLM-based methods. Better understanding of the evolution of the ictal BOLD signal is necessary to approach this task properly and the successful recording of seizures using simultaneous icEEG-fMRI is an invaluable development in realising this aim (Vulliemoz, Carmichael et al. 2011) and chapter 9.

7.5.2 Methodological considerations

7.5.2.1 Yield

Ictal EEG-fMRI studies have been rare as the recording of seizures during scanning is limited by the relatively short duration of the studies, patient safety and the unpredictability of events. This study is restricted to complete partial seizures which were successfully recorded in 9/101 unselected patients. All datasets were analysed regardless of motion. The yield is lower than reported in previous studies (Tyvaert, Hawco et al. 2008) (Donaire, Bargallo et al. 2009) or our more recent investigation (Chaudhary, Carmichael et al. 2012) most likely owing to the fact that the patients in this group were selected regardless of the degree of activity on the interictal EEG or seizure frequency rather than being restricted to those patients with frequent seizures.

7.5.2.2 Modelling technique

The exploratory approach resulted from the lack of an established, validated framework for mapping seizure related haemodynamic changes, particularly when using scalp EEG based models. Both GLM-based approaches were therefore implemented in a way that used the EEG more than simply to determine seizure onset and offset times for fMRI time series modelling. Importantly, both strategies to identify regions of ictal-
related BOLD signal change compared to baseline gave consistent results when more than one seizure was recorded. In those with multiple seizures (cases 3-6), this was done by representing individual seizures or electrically-defined parts of habitual seizures of the same type as instances of a single process, in the form of a single effect in the GLM which has the advantage of increasing statistical power.

In line with previous studies I have primarily assessed statistical significance of the SPM(F) of the combined phases and Fourier basis set contrasts based on the conventional, relatively conservative statistical threshold (p<0.05, Family Wise Error-corrected for multiple comparisons). This reflected the desire to validate fMRI as a whole-brain mapping technique without prior knowledge by comparing the findings with independently acquired electro-clinical data and as more appropriate given the small number of ictal events. For the individual ictal phases, in cases when no cluster survived correction I explored the data further by relaxing the threshold to p<0.001, uncorrected.

7.5.2.3 Modelling Approach: Block Design

I used a canonical GLM strategy representing a minimal set of assumptions between ictal EEG and BOLD at any given brain location: each EEG epoch is represented as a constant amplitude block and is convolved with the HRF derived from normal physiological processes (Friston, Frith et al. 1995). This simplistic model, with the inclusion of two additional regressors, the HRF time and dispersion derivatives, has been successfully used to reveal BOLD changes related to IED and to GSW discharges and absence seizures (Salek-Haddadi, Diehl et al. 2006). As a seizure is a dynamic process often evolving in different brain areas (Engel 1993) haemodynamic changes related three neurophysiologically informed phases were also investigated,
based on the observation that ictal EEG starts with a change from the baseline, evolving in amplitude and frequency represented as initial electrographic change (‘early ictal phase’), evolution of the seizure (‘clinical ictal phase’) and synchronised ictal discharges occurring most commonly as the seizure terminates (late ictal phase) (Verma and Radtke 2006). Modeling seizures as three phases assumes that the BOLD signal changes from one phase to another. Previous studies have divided seizures into blocks of uniform length (Donaire, Falcon et al. 2009, Tyvaert, LeVan et al. 2009), but I propose that a phasic model is a more physiologically informed approach, particularly given the variability in inter and intra subject seizure length. The approach could be further improved in the future by better models of features on the scalp EEG (for example modelling frequency specific BOLD signal change with a non-parametric function). In the individuals in whom it was not possible to distinguish all three phases on the scalp EEG I used a single block to represent the seizure (generally short seizures in which there was little benefit in sub-dividing the seizure given the temporal characteristics of the BOLD signal).

The degree of concordance of the results obtained with this modelling strategy, with 4 out of 7 cases analysed showing a map concordant with electro-clinical localisation of the ictal onset zone, confer it a level of validity

7.5.2.4 Assessment of concordance

Concordance was generally greater for the early ictal phase and for the map of the combined phases than for either the clinical and late ictal phases. In case #1, all single-phase maps were classified as discordant but the combined map was concordant. In another case (#4), the result for the early and clinical phases were concordant while the combined phases and late phase maps were discordant,
demonstrating that the F map for the combined phases was dominated by the late phase effect. These discrepancies result from the fact that the F contrast across all phases is based on the weighted sum of the individual effects and should therefore be the contrast of choice to answer the question “at which voxels do any linear combination (i.e. weighted sum) of the individual phases representing the seizure correlate with the signal?” The F contrasts for each individual phase should be used to answer the question: “at which voxels does the block representing the phase correlate with the signal?”.

Modelling the whole seizure by three neurophysiologically informed phases assumes that the level of the BOLD signal changes from one phase to another. Therefore, the SPM\{F\} obtained for all three phases together represents results of more physiologically plausible way of modeling than either modeling the whole seizure by one continuous block or modeling each phase independently of others what happens when SPM\{F\} is generated for each phase separately. Following that, it is not surprising that the SPM\{F\} representing BOLD signal changes for all three phases showed better concordance with ictal onset zone than SPM\{F\} built for each phase separately. The complex and inconsistent character of ictal haemodynamics across different patients with different types of seizures is well supported by the results of simultaneous optical and electrophysiological measurements (Zhao, Suh et al. 2007).

The degree of concordance with the seizure onset zone is lower than a more recent study from our group which improved the EEG model by the inclusion of more physiological confounds such as eye blinks and respiration (Chaudhary, Carmichael et al. 2012) which has been shown to improve sensitivity in EEG based GLMs of interictal data (Chaudhary, Rodionov et al. 2012).
It should be noted that the concordance scheme used in the ictal data is different from that applied in the comparisons of IEDs with intracranial data presented in chapters 6 and 10. This is because the ictal study was carried out prior to those studies and was not specifically designed to address the clinical role of EEG-fMRI. In addressing this issue, it became apparent that a revised concordance scheme was required to allow more meaningful clinical interpretation of the data.

7.5.2.5 Modelling Approach: Fourier basis set

Given the complexity of ictal haemodynamics, I chose to apply a second EEG-based model, allowing greater flexibility in the time course of BOLD signal change, using a Fourier basis set of regressors time-locked to events recorded on EEG. This approach aimed to increase the sensitivity of the model, given the uncertain nature of neurovascular coupling in epilepsy in general and seizures in particular. It also allows for wide variation in temporal patterns across space, but only signal change occurring between seizure onset and offset is recorded i.e. no post-event undershoot is modelled.

I was able to use this approach in three cases where the duration of a seizure was long enough (>3 TRs). To enable consistent BOLD patterns across events to be modelled, the longest epoch common to all events, commencing at seizure onset within a recording had to be used, a limitation which does not preclude the study of onset related BOLD signal change which is inherently interesting.

7.5.2.6 Independent Component Analysis

The approach to ICA of ictal fMRI used here employs Automatic component classification (De Martino, Gentile et al. 2007) reducing the number of candidate
'epileptic components' to a small subset of those generated by the decomposition algorithm having BOLD-like spatial and temporal characteristics in contrast to motion, vessels and noise. This approach effectively increases specificity by reducing the probability of finding an epileptic component by chance (i.e. a false positive). In our group's study of interictal fMRI (Rodionov, De Martino et al. 2007), epileptic components concordant with the IZ could be identified among the BOLD class of components in all cases. I took the same approach here, but also considered components classified as EPI artefacts to account for potential low-frequency ictal BOLD signal changes which have previously been observed. In contrast with the study of IED-related BOLD ICA for which EEG-based GLM maps were part of the validation, this study relies solely on spatial patterns. This is because I wanted to identify all spatially concordant ICs allowing further study of their temporal pattern particularly in relation to the simultaneously recorded EEG. In addition I have been able to use icEEG to validate our result in all but one case.

At least one IC in each dataset had a spatial distribution concordant with the localisation of the seizure onset zone derived from independent electro-clinical tests, including icEEG in 8 cases. Failure to identify potentially epileptic (ictal) components among BOLD and EPI components led me to inspect all 80 components in three cases (cases 3, 6, 9) to identify concordant components classified as not BOLD or EPI). In addition to reducing the technique’s specificity this raised the question of the true origin of those patterns. In cases 4 and 7, BOLD ICs were either misclassified by the automatic classifier as motion or contained artefactual components possibly due to sub-optimal decomposition. In these cases, I performed a secondary decomposition into 160 instead of 80 components.
In case 4, doubling the number of IC helped to “clean” the BOLD activity from
confounding factors which resulted in an IC classified as mixture of BOLD signal and
motion being spatially concordant with results of intracranial EEG. This case showed
the potential of ICA for analysing datasets contaminated by constant low amplitude
(less than 1 mm as seen on Table 7.1) motion which was characteristic for this
particular patient.

In case 7, the IC obtained following decomposition into 80 ICs was concordant with
ictal onset zone but heavily contaminated by artefact (most likely motion), as
suggested by the ‘striped’ appearance of the IC and high-frequency spikes on the IC
time course. A similar IC obtained from secondary ICA decomposition was classified as
motion. An additional IC also spatially concordant with ictal onset zone was observed
only in the decomposition with doubled number of IC. Although this IC was also
classified as motion its time-course suggested that this activity was misinterpreted
BOLD activity. Both IC were spatially concordant with the ictal onset zone also
covering the area adjacent to it, but a further cluster was noted in the right frontal lobe
which is unexplained. These results suggest that the optimal number of components
used in ICA may not have been successfully determined.

In cases 8, it was not possible to use EEG-based modelling of the three ictal phases as
the clinical seizures did not correlate well with scalp EEG change and data-driven
analysis of the fMRI was used. In these cases ICA revealed two and one respectively,
BOLD components that were concordant with the ictal onset zone, amongst X and Y
potentially epileptic components respectively.
7.5.2.7 Motion

I employed a modelling strategy that attempts to account for motion-related signal using a Volterra expansion of the six realignment parameters commonly used in fMRI studies. This is more comprehensive and therefore preferable in cases where motion is a highly significant confounding effect. The observed motion varied between cases and is given in Table 7.1.

Although I did not observe any correlation between the amount of motion and concordance of the BOLD clusters with ictal onset zone across all presented cases, it remains an important factor as (1) the approach to model ictal events prevails and requires further validation using direct measurements and (2) different types of motion (e.g. high/low amplitude, jerks/tremor/smooth) may have different impact on the results.

I did not use ‘scan nulling’ (Lemieux, Salek-Haddadi et al. 2007) as although this is effective in increasing sensitivity in interictal studies, scan nulling of the few recorded ictal events would result in severe distortion of the temporal evolution of the signal.

It could be suggested that datasets with significant motion would be uninterpretable as effects would be much more likely to reflect motion as opposed to haemodynamic effects. Surprisingly this does not appear to be the case; the pattern of BOLD signal clusters observed on the ictal SPM(F) was not typical of a motion-related change in all except one case (case 5) where head motion was particularly severe. In this case the widespread BOLD signal maximum was concordant with the ictal onset zone, perhaps due to the additive effect seizure related focal BOLD signal change and spatially uniform motion related signal change and consistent with the findings of ‘widespread intense BOLD signal change’ previously reported in ictal fMRI (Kobayashi, Hawco et al. 2006).
When using ICA, scan realignment was carried out and use of the automated classifier (De Martino, Gentile et al. 2007) enabled identification of high frequency noise reflecting motion without further pre-processing.

7.5.2.8 Limits of fMRI study

No significant ictal BOLD signal change was observed in either of the temporal lobe epilepsy cases (6 and 9), which may reflect EPI signal dropout in these regions. This highlights the difficulty of interpreting negative fMRI results since the possible explanations include weak correlation of putative BOLD signal variations with the effect of interest and a weak signal to noise ratio.

7.5.3 Significance of results

7.5.3.1 General Linear Model

Significant ictal-EEG related BOLD signal changes were revealed in 6/9 cases (6/7 cases for where the EEG could be modelled). The BOLD patterns were concordant with the ictal onset zone in 4 cases. All 4 patients had neocortical epilepsy and in addition, the earliest EEG change was easily identified and accurately reflected the timing of seizure onset recorded on depth electrodes (assessed by comparison of scalp and intracerebral video-EEG).

In contrast, in case 9 in no ictal BOLD signal change was observed, and in cases 4, 6 and 7 no early ictal correlated BOLD signal change was observed concordant to the seizure onset zone. Here, EEG change was more difficult to discern owing to underlying abnormal background (case 4) or the scalp EEG not accurately reflecting seizure onset, which illustrates a key limitation in the use of ictal EEG-fMRI data.
The Fourier basis set model revealed involvement of wider (case 1) or additional (cases 3, 7) brain areas compared with the canonical HRF model, and the overall degree of concordance was similar for the two models. The additional BOLD cluster revealed in case 3 compared to the map obtained from the canonical model, although not close to the structural lesion corresponded well to one of the IC exhibiting haemodynamic activity time-locked to the ictal event on EEG. High-amplitude signal fluctuations in the Fourier model-derived clusters were suggestive of motion-related effects. However, their spatial distribution was more typical of a focal BOLD response rather than the generally widespread pattern seen in motion and the corresponding time-course was reminiscent of BOLD signal changes rather than sharp changes due to motion.

The clusters of BOLD signal change in case 7 were not concordant with ictal onset zone. However, the patient was not seizure free after surgery which might encourage further investigation of the left occipital cluster.

In case 8, the results presented are based on an EEG derived model, which shows similar activity to that observed during ictal events, but not always correlated with clinical seizures. This patient experienced repeated clinical seizures and clonus in the left foot during recording, and the BOLD activation was concordant with the seizure onset zone when EEG events typically correlated with these episodes were modelled.

7.5.3.2 Significance of the ICA results

We identified ICs spatially concordant with ictal onset confirmed on intracranial EEG in all except 1 case. Comparison of the ictal IC with the GLM results showed a similar degree of concordance for the two GLM approaches. Some of the discrepancies between the ictal IC and GLM results may result from the spatial smoothing applied to
the fMRI in the GLM. More importantly, the differences probably reflect the fundamentally different nature of the two analysis frameworks, the GLM approach being based on identifying correlates of EEG events whereas ICA identifies patterns based on separating independent signals.

In 5 out of 9 cases, the IC concordant with the ictal onset zone had been classified as BOLD. In one case (case 7) the classification was ‘EPI’ meaning the classifier identified fMRI signal in the lower frequency range. It may be that this component was classified as EPI, as the automated tool recognises all low frequency signal as EPI signal drift, regarding as ‘noise’. This noise is often seen at the grey matter-CSF or brain-air interface (e.g. basal temporal lobes and frontal lobes close to the mouth or sinuses), but in this case the spatial pattern was markedly different from the typical EPI signal drift. It is possible that this low frequency signal is in fact a marker of epileptic activity as has been observed in other studies which component on slow frequency fMRI in ictal data.

In the 3 remaining cases the ictal IC were classified as artefactual confounds (case 3: motion, case 6: spatially distributed noise, case 9: temporal high frequency noise). Clusters on the IC maps were all very focal and spatially concordant with the ictal onset, however and one explanation for this is that they represent inadequately separated components, as during seizures, neural activity is typically correlated with motion.

These ‘non-BOLD’ components which were concordant with seizure onset demonstrate a drawback of using the classifier- that it is trained on normal physiological data. I anticipate that refinements to the ICA method (Valente, De Martino et al. 2009) and
specifically training a classifier on ‘epileptic data’ might result in greater sensitivity to
‘epileptic components’.

7.5.3.3 Pre-ictal changes

Visual inspection of the IC signal time course was concordant with seizure onset in 5/9
cases. In all 5 cases, I observed rhythmic BOLD signal fluctuations up to 7 minutes
prior to the onset of the seizure on scalp EEG. This is in line with evidence from
simultaneous scalp EEG + optical, and scalp + intra-cranial EEG recordings as well as
fMRI studies in both animals and humans (Suh, Ma et al. 2006) and has been
described as a pre-ictal state (Zhao, Suh et al. 2007). Evidence from intracranial EEG
and other modalities also suggest that there may be changes in both neuronal and
haemodynamic activity within and around the ictal onset zone up to minutes prior to
seizure onset and our data supports this. There are various hypotheses for the
underlying cause of these changes. Zhao and colleagues have recently shown, in an
elegant experiment, that there are abnormalities in cerebral tissue metabolism which
occur around the time of seizure onset and that this is preceded by local
vasoconstriction of arterioles surrounding (but not within) the ictal focus, which might
explain some of the preictal abnormalities seen in fMRI studies (Zhao, 2011 #2197,
Zhao, Nguyen et al. 2011). They hypothesised that this vasoconstriction effectively
‘shunts’ blood to the metabolically active seizure onset zone (resulting in a centrally
active region with ‘surround inhibition’similar to that described both the irritative zone
and normal cortical processing) and raised the possibility that haemodynamic changes
rather than electrographic in the ictal focus might be a primary event in seizures, which
has also been argued for interictal haemodynamic changes (Hawco, Bagshaw et al.
2007).
Other possible explanations for a ‘pre-ictal state’ include the possibility that increased neuronal synchrony at this time is not specific to seizures, but reflects a change in state which may promote, but does not cause seizures per se following observations from objective analysis of EEG signal both with and without ictal EG patterns (Navarro, Martinerie et al. 2005). Other measures of EEG activity such as high frequency activity may provide further insight into this ‘pre-ictal’ haemodynamic state, particularly given that BOLD is most closely coupled with local field potentials which in themselves reflect higher frequency oscillations which are seen at ictal onset on depth electrodes (Bourien, Bartolomei et al. 2005) (Bartolomei, Wendling et al. 2001) (although we did not see this fast activity until seconds before the clinical ictal onset during icEEG recordings). In case 8, the EEG did not reflect clinical seizure pattern, making it impossible to comment on the temporal relationship between BOLD signal and seizures. In the three cases (4, 6 and 7) in which the relationship between IC time course and EEG event seemed less clear these may have been masked by the effects of motion.

7.5.3.4 Clinical Significance

All studies of ictal fMRI data have suggested it is possible to observe BOLD signal change correlated either with clinical or electrographic seizures (Detre, 1995 #814)(Federico, Abbott et al. 2005, Kobayashi, Hawco et al. 2006, Tyvaert, Hawco et al. 2008, Donaire, Bargallo et al. 2009, Tyvaert, LeVan et al. 2009) using forms of the GLM in which scalp EEG change is convolved with an HRF. Although the GLM is a useful model when the scalp seizure onset accurately reflects true seizure onset, the results here suggest that a data-driven method such as ICA is able to demonstrate BOLD signal IC which are concordant with the ictal onset zone recorded on icEEG
even when there is not an adequate EEG derived model. This suggests a potential role for ICA in planning icEEG in some patients.

### 7.5.4 Further Work: Implications for this study

This work is one of the larger series of ictal data acquired with EEG-fMRI and the approach is necessarily exploratory. I was only able to capture seizures in a small group of patients. Subsequently, Chaudhary and colleagues were able to capture seizures in 22 patients and extended the work presented here by looking specifically at the patterns of BOLD signal change occurring in the pre-ictal period, which were hinted at in the above experiment (Chaudhary, Carmichael et al. 2012). This study also refined the EEG model and sought to apply a more clinically appropriate classification of concordance. A specific development which may have improved the yield and degree of concordance observed in the work presented here is the evolution of simultaneous video EEG-fMRI which allows more comprehensive classification of seizures and a more accurate measurement of seizure onset (Chaudhary, Kokkinos et al. 2010). This is particularly relevant to case 4 in whom the clinical seizure onset appeared to occur prior to any scalp EEG change when icEEG was performed. I have also subsequently recorded a seizure in a single patient undergoing intracranial EEG-fMRI, the results of which are presented in Chapter 9.

### 7.5.5 Conclusion

The analysis and interpretation of fMRI data acquired during seizures with concurrent EEG requires careful consideration in view of the limitations of scalp EEG as a marker of ictal activity. Two EEG-based models were successful in revealing significant BOLD changes in the majority of cases and the results of the two methods were broadly in agreement. In this small group of cases, the number of seizures captured, location of
the ictal onset zone and amount of head motion had an important impact on BOLD localisation and chances of obtaining meaningful BOLD maps. In cases with single ictal events a refined data-driven approach such as ICA can provide valuable, independently verified information regarding the ictal onset zone validated by intracranial recording as well as a basis for studying the dynamics of ictal related BOLD signal change. Concordance of the ICA and icEEG findings suggests a potential role of ICA in planning invasive investigations.

Flexible data-driven approaches are potentially useful for studying ictal fMRI data. However, they require good knowledge of ictal hemodynamics to be properly assessed for practical use.
8 EXPERIMENT 4: WHAT CAN EEG-FMRI TELL US ABOUT THE DYNAMICS OF THE EPILEPTIC NETWORK? A STUDY COMPARING DYNAMIC CAUSAL MODELING FOR FMRI WITH INTRACRANIAL EEG.

8.1 Summary

Background and Aim

In both the pilot and FCD studies (chapters 5 and 6) I found that there are often multiple regions of BOLD signal change associated with each type of IED in line with previous studies discussed in chapter 2.13.4. Comparison with ESI suggests that these regions of activation may correspond to spike initiation and propagation (Groening, Brodbeck et al. 2009, Vulliemoz, Lemieux et al. 2010), but there have, to date, been few attempts to try and ascertain if it is possible to infer causal relationships between regions involved in the epileptic network from fMRI data. Dynamic Causal Modelling is a method of measuring ‘effective connectivity’ between two or more regions of BOLD signal change and models hidden neuronal states allowing inferences regarding the causal relationships between neuronal populations underlying the regions (Friston, Harrison et al. 2003). I aimed to investigate whether DCM of IED-related fMRI reflected functional connectivity between regions giving rise to populations of interictal spikes on icEEG. I also sought to compare the results of interictal fMRI DCM with ictal icEEG patterns, using both non-linear correlation analysis at seizure onset and patterns of seizure propagation as a neurophysiological validation.

Materials and Methods:

Patients were identified from the cohort described in section 2 with >1 region of IED correlated BOLD signal change or a large region of BOLD signal change who
subsequently underwent intracranial EEG recording and in whom electrodes within the irritative zone were colocalised with regions of IED related BOLD signal change (n = 6).

In the first instance, patient-specific models were defined based on regions of interest covered by both fMRI activation and icEEG spikes. IEDs were defined as driving input on each ROI or modulatory input on inter-nodal connections and Bayesian Model Comparison used to identify the best model given the data. The regions of interest were verified by identifying sets of co-activated structures in the irritative zone and a directionality index was calculated at seizure onset between the same structures in order to validate the fMRI model. Results were also compared with patterns of seizure propagation on icEEG. Following this I sought to apply a more complex fMRI-DCM model comparison to the data in one patient.

**Results:**

6 patients had more than one region of IED-related BOLD signal change corresponding to the IZ as identified on subsequent icEEG. In 5/6 patients DCM applied to regions of IED-related BOLD signal change recorded on interictal scalp EEG-fMRI, matched patterns of seizure propagation observed on icEEG. In the remaining patient it was not possible to identify a single model as the ‘best fit’. In all patients who underwent stereo encephalography (sEEG), sets of co-activated structures (SCAS) were identified on interictal icEEG, which were concordant with the regions of IED-related BOLD signal change. In 3/4 of these patients, the ‘direction index’ at seizure onset identified a ‘leading region’, which corresponded to that identified from the fMRI data. In the remaining patient a clear leading region in the epileptic network could not be identified from analysis of the ictal data. A further fMRI-DCM analysis in one patient, designed to
assess complex network dynamics more comprehensively was also in agreement with icEEG data.

Conclusion:

fMRI DCM applied to IED-related BOLD signal change appears to be able to predict patterns of seizure propagation on intracranial EEG. This suggests that fMRI-DCM is a valid approach for investigating epileptic networks and furthermore it may be a useful addition to understanding interactions between task related neuronal activity and epileptic networks in focal epilepsy (although the approach used here is limited by the need to compare sequentially acquired data and methodological limitations in both fMRI-DCM and icEEG analysis).

8.2 Introduction

The investigation of focal epilepsy has traditionally been based on the identification of discrete ‘zones’ corresponding to regions of cortex generating interictal discharges (IEDs) or ‘spikes’ (the irritative zone) and those regions which generate seizures (the seizure onset zone). Increasingly, it is recognised that this understanding of focal epilepsy is simplistic and that there is a network of brain regions involved in the generation of seizures (Bartolomei, Wendling et al. 2001, Spencer 2002, Laufs 2012). Studies of particular epilepsy syndromes using stereo encephalography (sEEG) based on the methods pioneered by Bancaud and Talairach in the 1950s have identified many of these regions and measures of correlation between regions involved in the irritative zone as well as those regions with ‘epileptogenic’ tissue have been used more recently to understand the way in which these networks are formed (Bartolomei, Wendling et al. 2001, Wendling, Bartolomei et al. 2001, Aubert, Wendling et al. 2009,
Bartolomei, Cosandier-Rimele et al. 2010). In particular the group that pioneered many of these studies showed that functional connectivity at seizure onset increased within the epileptic network and using a directionality index, they could infer causal relationships between nodes in the epileptic network in both simulated data and patients with temporal lobe epilepsy undergoing sEEG (Wendling, Bartolomei et al. 2001).

It is well recognised in conventional IED related analysis of EEG-fMRI data, that in addition to IED-related BOLD signal change colocalised with the seizure onset zone, additional clusters of IED-related BOLD signal change in close proximity as well as remote from the seizure onset zone are often revealed and investigation of these patterns with electrical source imaging has been helpful as discussed in section 2.13.4. In addition, I have shown by comparison with iEEG, that regions of IED-related BOLD signal change may be co-localised with both the irritative and seizure onset zones within the epileptic network (Grouiller, Thornton et al. 2011, Thornton, Vulliemoz et al. 2011) (also see Chapter 6).

Remote regions of IED related BOLD signal change may occur owing to physiological phenomena (e.g. changes in resting state networks (Archer, Abbott et al. 2003, Hamandi, Salek-Haddadi et al. 2006, Laufs, Hamandi et al. 2007)), artifact, (Lemieux, Laufs et al. 2008), or spike propagation (Boor, Jacobs et al. 2007, Groening, Brodbeck et al. 2009, Vulliemoz, Lemieux et al. 2010). This is not surprising given that in cognitive studies, both block and event related designs do not reveal single areas of BOLD signal change, but rather a network of activated brain regions about which inferences about the structure and in particular, function of cognitive networks can be drawn (Raichle and Snyder 2007). In addition to identifying these networks fMRI experiments have demonstrated altered connectivity between brain regions, both within
and outside the ‘epileptic network’ in patients with focal epilepsy, which appear to alter over time (Morgan, Gore et al. 2010, Morgan, Rogers et al. 2011, Vollmar, O’Muircheartaigh et al. 2011).

In order to evaluate the behaviour of any cerebral network, however, it is important to be able to demonstrate directionality and causal relationships within the networks, allowing inferences regarding the influence of one brain region over another. In the case of generalised spike and wave activity, in which corticothalamic networks have been well documented for many years (Avoli and Gloor 1982), DCM has been used to evaluate causal relationships within cognitive (Friston, Harrison et al. 2003) and more recently epileptic networks both in animal models, validated with icEEG (David, Guillemain et al. 2008) and in humans (Vaudano, Laufs et al. 2009). In focal epilepsy, single case reports suggest DCM of both IED-related fMRI (Hamandi, Powell et al. 2008, Murta, Leal et al. 2012), is feasible and may give some information about epileptic networks, but the approach has not been formally validated with intracranial data.

In this experiment, I undertook a prospective study of fMRI-DCM in epileptic networks in focal epilepsy compared with icEEG using a functional connectivity analysis of interictal spikes and non-linear correlation analysis of ictal activity at seizure onset as well as observation of seizure propagation patterns on icEEG. Following developments in DCM methodology, I also undertook a further comparison of families of models in a single case, which allows increased number and more complex models to be explored including allowing the specification of IEDs as a modulatory input (i.e. on inter-regional connections). This is discussed further in the context of the methods and discussion below.
8.3 Materials and methods

8.3.1 Patient Selection:

Patients were recruited as described in section 3.1.1. 32 patients had IED-related BOLD signal change at the time of this experiment and 6/32 had both more than one cluster of BOLD signal change corresponding to regions covered by icEEG electrodes and within the ‘epileptic network’ defined on subsequent icEEG and were selected for this analysis.

8.3.2 Clinical Evaluation:

Patients underwent electro-clinical assessment as described in section 3.1.3. IcEEG was carried out for each patient according to local protocol and the IZ, SOZ and EZ were identified by the patient’s clinical team.

8.3.3 EEG-fMRI Acquisition

All patients underwent EEG-fMRI as described in section 3.1.4.

8.3.4 fMRI processing and analysis:

The fMRI time-series were realigned, spatially smoothed with a cubic Gaussian Kernel of 8 mm full width at half maximum and analysed using a general linear model (GLM) in SPM8 (www.fil.ion.ucl.ac.uk/SPM) to identify IED-related BOLD changes. We used SPM 8 (released in 2009) for this experiment as it contains more sophisticated neuronal models for the DCM analysis in contrast to SPM5, which was used in the earlier experiments. Separate sets of regressors were formed for each type of IED allowing identification of specific BOLD effects. Discharges were represented as zero-duration events (unit impulse, or ‘delta’, functions) convolved with the canonical
haemodynamic response function its temporal and dispersion derivatives, resulting in three regressors for each event type (Friston, Fletcher et al. 1998). Motion-related effects were included in the GLM as 24 regressors representing 6 scan realignment parameters and a Volterra expansion of these (Friston, Williams et al. 1996). Additional regressors were included for pulse-related signal changes (Liston, Lund et al. 2006).

F-contrasts were used across three regressors corresponding to each event type with a threshold of p<0.05 corrected for multiple comparisons (family-wise error) considered significant. EPI data were co-registered to the pre-operative T1-weighted images to create activation map overlays (Ashburner and Friston 1997). Clusters of significant BOLD change were labelled anatomically on high resolution EPI images and co-registered with structural T1 images.

8.3.5 Intracranial EEG recording:

Patients underwent intracranial EEG recording according to clinical criteria and local protocol. All recordings were undertaken with standard macro electrodes arranged in sub-dural grids, depth electrodes (sEEG) or a combination of the two methods with between 18 and 72 recording electrodes per patient. Intracranial EEG was inspected by two trained observers (RT and one of the patient’s clinical team) and electrodes identified as ‘irritative zone’ (electrodes from which spikes were recorded), ‘seizure onset zone’ (electrodes at which the onset of low amplitude fast activity was observed at seizure onset) and ‘region of propagation’ (electrodes to which the seizure propagated within 2 seconds).
8.3.6 Comparison of fMRI regions with intracranial EEG recording

Patient-specific T1-weighted MRI scans obtained during the EEG-fMRI recording were co-registered and fused with a post-implantation CT with the sub-dural grid or depth electrodes in situ (Winkler, Vollmar et al. 2000) using the same method as that described in section 3.1.9. These fused images were co-registered with the SPM(F) to identify regions of BOLD signal change in relation to the intracranial EEG in the same way as previous experiments described in chapter 3.

8.3.7 Dynamic Causal Modelling (all in SPM 8):

8.3.7.1 Simple model

1. **Specification of the regions of interest:** Regions of interest were defined based on the comparison of the GLM results and icEEG as follows. Each cluster of significant IED-related BOLD signal change overlapping at least one icEEG electrode located in the IZ was specified as a ROI for the model. fMRI time series were extracted for each node in the network.

2. **Specification of the model:** Bidirectional connections were specified between all identified ROIs in each network as well as connections within each ROI. Interictal events (IEDs) recorded on scalp EEG during EEG-fMRI recordings were specified as a ‘driving input’ on each node in the network resulting in up to 3 different models (see Figure 8-1 for an example).

3. **Model Comparison:** Bayesian model comparison was used to assess the log evidence for each model giving a probability of each model given the ‘priors’ of the anatomical network and occurrence of the interictal discharge within SPM 8. When the log evidence of one model compared with another was calculated in
SPM 8 \((\ln p(y|m_1) - \ln p(y|m_2))\). A difference between the models of around 3 (i.e. \(p < 0.05\)) was considered significant and the model with the highest probability was identified as the most likely, given the data.

**Figure 8-1:** Examples of models with bidirectional coupling for a 3 node network.

IEDs (top) are specified as driving input to each region within the network.

### 8.3.8 Family model approach

In a single case (case 1), I undertook an exploratory analysis allowing comparison of different coupling between regions and also used a further Bayesian Model Comparison to repeat the previous analysis on the two resulting ‘families’ of models specific to each possible node. This follows observations that this method allows the rapid comparison of more models including allowing for the possibility that IEDs act as
modulatory input on connections between regions of interest as well as comparing models with both uni and bidirectional couplings (Murta, Leal et al. 2012) as well as recent developments to the DCM approach. I hypothesised that this was a more physiologically plausible approach and allowed greater flexibility.

1. **Regions of interest** were identified using the approach described above.
2. **Specification of the models:** Families of different physiologically plausible models with uni or bidirectional couplings were defined and IEDs specified as either driving or modulatory input enabling 14 different models of the network dynamics to be tested, resulting in two families of 14 models each, on for each cortical region. I did not include the thalamus as a possible site for the driving input as there was no evidence for this in the first experiment. An example of the models for case 1 is given below.

3. **Model Comparison:** The 14 possible models for each node were compared in SPM8 using Bayesian model comparison and the model with the highest log evidence identified as the most likely given the data. The two families of models were compared using Bayesian Model Comparison in SPM8 and the model most likely to explain the data identified by calculating the log evidence and posterior probability of each model given the data.
Networks were defined with uni or bidirectional couplings at each pair of nodes and for each network 2 models were considered: one where IEDs were only specified as direct input on the ‘driver of the network’ (red arrow) and the other with IEDs specified as modulatory input. 14 physiologically plausible models were identified in this way.

8.3.9 Analysis of the icEEG:

The intracranial EEG recordings were analysed using a lag correlation analysis described previously (Bourien, Bartolomei et al. 2005). Briefly, spikes were selected over a five minute period matched to the EEG-fMRI recording for sleep state by using automatic spike detection software in all electrodes. The electrodes giving rise to interictal spikes (IS) in closest proximity to each region of IED-related BOLD signal change in the fMRI-DCM network were identified. Subsets of coactivated structures were identified as described elsewhere (Bourien, Bartolomei et al. 2005).

In patients in whom this approach has not been possible (those with grid electrodes in whom the approach is not valid, patients 5 and 6), as well as those in whom the analysis was carried out, we also analysed the pattern of seizure propagation.
8.3.9.1 Details of the Automatic Spike Detection Method and identification of Functionally connected regions

- Detection of interictal spikes (IS) on icEEG data

In order to detect IS, we used an algorithm implemented in the ‘Amadeus’ programme using Deltamed software which is described in detail elsewhere (Bourien, Bartolomei et al. 2005). This method starts from the fact that interictal epileptic spikes include a “sharp” component corresponding to a transient wave of high amplitude and short duration compared to background activity. This component is characterized a specific signature in the time-frequency plane, i.e. an increase of energy in higher frequency bands (typically from 20 to 40 Hz).

For each patient, results were inspected by an epileptologist to ensure the interictal spikes identified were ‘true’.

2. Identification of co-activated structures

Following this subsets of coactivated structures (SCAS) were identified using further algorithms within the Amadeus programme (Bourien, Bartolomei et al. 2005) to identify pairs of structures, which are functionally connected during interictal epileptiform activity. The reason for this was to verify that the regions of interest identified for DCM analysis corresponded to the epileptic network identified on intracranial EEG.

8.3.9.2 Non-linear correlation analysis of spiking activity at seizure onset

Following detection of interictal spikes in two or more coupled regions, I used a non-linear correlation analysis to calculate functional connectivity, ‘h2’ and ‘direction index’ (D) between the same regions at seizure onset, a method which has been used in temporal lobe epilepsy to identify propagation patterns at seizure onset within the epileptic network (Wendling, Bartolomei et al. 2001). Pairs of electrodes were
compared and one electrode identified as the 'leading' region from the pairs for the period of time at which low amplitude gamma frequency 'spiking' activity occurred. This was repeated for each pair of nodes specified in the model.

The reason behind the development of this method was to investigate seizure dynamics but also because it can be difficult to identify which region drives fast (gamma band) activity at seizure onset, when it may appear to arise in more than one coupled region (see Figure 8-3).
Figure 8-3 Typical evolution of a seizure on icEEG.

Note the almost simultaneous onset of rapid spiking activity in the electrodes at the top and bottom of the trace (Top = right parafusiform gyrus (PFG), bottom = left parafusiform gyrus (PFG'), fast activity also seen at the hippocampus (B) and occipto-temporal junction (OT)).

Owing to the fact that this method was developed for simulated and real sEEG data (i.e. data measured from depth electrodes only), I did not apply the approach to those patients in whom sub-dural grids were used.

8.3.9.3 Qualitative Analysis of Seizures

The final part of the analysis was to inspect the sEEG seizure pattern to identify in which electrodes the seizure onset zone occurred, and the pattern of propagation. The electrodes were defined at that which low amplitude high frequency (gamma or above).
was first seen at seizure onset (verified by the clinical team and myself as the seizure onset zone from review of intracranial video-EEG). Regions of rapid propagation were defined as those electrodes to which electrographic seizure activity spread within 2 seconds of seizure onset.

8.4 Results

8.4.1 Patients and results of GLM analysis:

37 of the 101 patients who formed the cohort recruited for this study had IEDs recorded during EEG-fMRI sessions. In six of these patients analysed in SPM8 at least 2 regions of IED-associated BOLD signal change were observed which colocalised with one or more electrodes at which interictal spikes (IS) were recorded on intracranial EEG and these were selected for DCM analysis (see Table 8.1 for electro-clinical details of the patients). Three had frontal lobe epilepsy, 2 had posterior epilepsy (1 biparietal, 1 temporo-parieto-occipital) and the remaining patient has right neocortical temporal lobe epilepsy. The results in SPM8 were comparable with those in SPM5 (used in earlier sections, but are given in along with brief clinical details, for clarity).
<table>
<thead>
<tr>
<th>1</th>
<th>RFLE</th>
<th>RF atrophy</th>
<th>BiF spike and wave</th>
<th>Yes</th>
<th>Head version to L, dysphasia, L clonic movements</th>
<th>8x 10c RH depth electrodes 1x oblique electrode</th>
<th>R PF, R PM, R thal, R OF</th>
<th>R OF, R PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>RTPL E</td>
<td>R TPO FCD</td>
<td>R temporoparietal polyspikes</td>
<td>Yes</td>
<td>Loss of awareness, automatism, vocalisations</td>
<td>9x 10c RFTP tangential depth electrodes</td>
<td>R Cu, R InfT, R OT, R LingGy, R Am, RH</td>
<td>R basal T extensive</td>
</tr>
<tr>
<td>2b</td>
<td>RTPL E</td>
<td>R temporoparietal spikes</td>
<td>No</td>
<td>Loss of awareness, automatism, vocalisations</td>
<td>9x 10c RFTP tangential depth electrodes</td>
<td>R Cu, R InfT, R OT, R LingGy, R Am, RH</td>
<td>R Inf T extensive</td>
<td>R Cu, ROT</td>
</tr>
<tr>
<td>3</td>
<td>RFLE</td>
<td>Normal</td>
<td>R central spikes</td>
<td>Yes</td>
<td>Clonic movements R foot, paraesthesia, tonic</td>
<td>3x 15c R pericentral depth electrodes, 1x15c R mes frontal</td>
<td>R Pre-central gyrus, R post central gyrus, R pericentral region</td>
<td>R parietal</td>
</tr>
</tbody>
</table>

Abbreviations: R= right, L=left, F= frontal, Inf = inferior, T= temporal, P= parietal, OF= orbitofrontal, PM = pre-motor, PF= pre-frontal, Cu= cuneus, Ling = lingual, Am = amygdala, OT = occipito temporal, SMA = suplimentary motor area, H= hippocampus, G = gyrus, c= contact,
<table>
<thead>
<tr>
<th>No.</th>
<th>Region</th>
<th>Side</th>
<th>Finding</th>
<th>Symptom &amp; Description</th>
<th>Electrodes</th>
<th>Electrode Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Bi Post E</td>
<td>R Post FCD/atrophy</td>
<td>RP polyspikes</td>
<td>Yes</td>
<td>Paraesthesia left side, bizarre vocalizations, hypermotor activity</td>
<td>8x 10-15c RH depth electrodes, 1x 15c depth electrode to L post fusiform gyrus</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>R TP spikes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>RTLE</td>
<td>Normal</td>
<td>R posterior temporal spikes</td>
<td>Yes</td>
<td>Loss of awareness, oral automatism</td>
<td>32 contact grid over the R temporal lobe, 2x 6c depth electrodes to RH and RA.</td>
</tr>
<tr>
<td>6</td>
<td>LFLE</td>
<td>L middle frontal gyrus FCD</td>
<td>L mesial frontal spike and wave discharge</td>
<td>Yes</td>
<td>R head version, loss of awareness</td>
<td>48c LF grid, 16 c LFT grid, 2x tangential 6c L frontal depth electrodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: R= right, L=left, F= frontal, Inf= inferior, T= temporal, P= parietal, OF= orbitofrontal, PM= pre-motor, PF= pre-frontal, Cu= cuneus, Ling= lingual, Am= amygdala, OT= occipito temporal, SMA= supplementary motor area, H= hippocampus, G= gyrus, c= contact,
Figure 8-4 Patient 1: IED-related GLM result in SPM8 overlaid on fused T1 weighted MRI with CT with electrodes in situ.

p<0.05 FWE corrected for multiple comparisons. Each region of IED-related signal change which colocalised with an electrode in the irritative zone was selected as a region of interest. Right medial orbitofrontal cortex and dorso lateral pre-motor cortex indicated by arrows.

8.4.2 Results of fMRI DCM (all carried out as implemented is SPM8):

1. Identification of regions of interest and model specification: Regions of interest (ROIs) identified according to the criteria given above as well as model specifications are given in Table 8.2. All models included bidirectional coupling as discussed in the methodology similar to the example in Figure 8-1.

2. Results of the DCM analysis are given in Table 8.2 In all cases, the ‘best model’ is that for which the difference in log evidence was 3 or greater. Models with a
log evidence of <3 were considered to be equally likely. An example of the
model specification and DCM result is given in figure 8.5.

Figure 8-5 Example of model specification and posterior probability of each
model

Abbreviations: R= right, OF= orbito-frontal cortex, PreM = lateral pre-motor cortex, Th = thalamus, IEDs= interictal epileptiform discharges.

Case 1. DCM favoured a single model. a. Regions of interest and coupling, b. Models specified for input to DCM. C. Log evidence for each model given the
data (top) and posterior probabilities of each model given the data (bottom).
### Table 8.2 Results of IED-related GLM and fMRI DCM analysis

<table>
<thead>
<tr>
<th>Type</th>
<th>Events modelled</th>
<th>Summary of IED-related GLM SPM(F) p&lt;0.05 FWE corrected</th>
<th>Models specified***</th>
<th>Results of DCM*</th>
<th>Results of icEEG analysis**</th>
<th>Seizure propagation pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RFL E</td>
<td>BiF SpW</td>
<td>R OF</td>
<td>1. IED→ROF</td>
<td>2&gt;1&gt;3</td>
<td>R PreF/OF→RPreM=Th</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R Th (-)</td>
<td>2. IED→RPreM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lat PreM</td>
<td>3. IED→RTh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RTP LE</td>
<td>R TP polysp</td>
<td>R inf TL</td>
<td>1. IED→RinfTL</td>
<td>1&gt;2=3</td>
<td>R InfT→RHc→ROccLo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R ACC</td>
<td>2. IED→RHC</td>
<td></td>
<td>R InfT→RInfT→ROccLo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R occ</td>
<td>3. IED→ROccLo</td>
<td></td>
<td>RHC→RInfT→ROccLo</td>
</tr>
<tr>
<td>3</td>
<td>RPL E</td>
<td>R central spikes</td>
<td>R pre-CG</td>
<td>1. IED→RPa</td>
<td>1&gt;2=3</td>
<td>R PreCG=RPa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R SMA</td>
<td>2. IED→RPreC</td>
<td></td>
<td>R PreCG→RSMA &amp; RPa</td>
</tr>
<tr>
<td>4</td>
<td>Bi Post E</td>
<td>RP polysp</td>
<td>RP</td>
<td>1. IED→RPa</td>
<td>1&gt;2=3</td>
<td>R Pa&gt;LPa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LP</td>
<td>2. IED→LPa</td>
<td></td>
<td>RPa→LPa &amp; LPa</td>
</tr>
<tr>
<td>5</td>
<td>RTL E</td>
<td>R post T spikes</td>
<td>R Post T</td>
<td>1. IED→RPostT</td>
<td>1&gt;2</td>
<td>N/A (sub-dural grids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RH</td>
<td>2. IED→RAntHc</td>
<td></td>
<td>RPostT→RHc</td>
</tr>
</tbody>
</table>

Abbreviations: R= right, L= left, F=frontal, T= temporal, P= parietal, Occ= occipital, PreM = pre-motor cortex, OF= orbito-frontal,, C= central G= gyrus, Inf= inferior, Th= thalamus, H= hippocampus, Lo= lobe, M= middle, E= epilepsy, ant= anterior, S = superior, IEDs= inter-ictal epileptiform discharges, SpW = spike and wave discharges, Pa= parafusiform gyrus, med = medial, Post = posterior, *Log evidence of a given model is greater (difference more than 3) than another to be considered significant = denotes a difference between two models of <3. **Non-linear correlation analysis of ‘spiking activity’ at ictal onset. ***All models have bidirectional coupling as in example figure 8.1.
<table>
<thead>
<tr>
<th></th>
<th>LFLE</th>
<th>L med F SpW</th>
<th>L MFG</th>
<th>L SFG/Pr eCG</th>
<th>L IFG</th>
<th>1. IED→LSFG</th>
<th>2. IED→LPreCG</th>
<th>3. IED→LinFG</th>
<th>1=2</th>
<th>1&gt;3</th>
<th>2&gt;3</th>
<th>N/A (sub-dural grids)</th>
<th>LSFG→LPreCG →LinFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. IED→LSFG</td>
<td>2. IED→LPreCG</td>
<td>3. IED→LinFG</td>
<td>1=2</td>
<td>1&gt;3</td>
<td>2&gt;3</td>
<td>N/A (sub-dural grids)</td>
<td>LSFG→LPreCG →LinFG</td>
</tr>
</tbody>
</table>

Abbreviations: R= right, L= left, F=frontal, T= temporal, P= parietal, Occ= occipital, PreM = pre-motor cortex, OF= orbito-frontal, C= central G= gyrus, Inf= inferior, Th= thalamus, H= hippocampus, Lo= lobe, M= middle, E= epilepsy, ant= anterior, S = superior, IEDs= inter-ictal epileptiform discharges, SpW = spike and wave discharges, Pa= parafusiform gyrus, med = medial, Post = posterior, *Log evidence of a given model is greater (difference more than 3) than another to be considered significant = denotes a difference between two models of <3. **Non-linear correlation analysis of 'spiking activity' at ictal onset. ***All models have bidirectional coupling as in example figure 8.1.
8.4.3 Intracranial EEG details:

Each patient had icEEG according to local protocol. Patients 1-4 all underwent sEEG using multiple 10-15 contact depth electrodes while patients 5 and 6 underwent icEEG using a combination of sub-dural grid electrode arrays and depth electrodes. Details of the intracranial EEG are given in Table 8.1.

8.4.4 Concordance of DCM models with icEEG:

1. icEEG sets of coactivated structures

In 4 of 6 patients (patients 1-4), sEEG showed interictal spikes recorded at electrodes colocalised with the fMRI-ROIs and analysis of the signals recorded at these structures, following automatic spike detection over a 30 minute icEEG epoch, resulted in the identification of coactivated structures which corresponded to all the identified ROIs (seeFigure 8-6 for an illustration of the results of this analysis). In the remaining 2 patients, sub-dural grid electrodes were used and so the same analysis was not performed.
Figure 8-6: Example of identified sets of coactivated structures.

Labels refer to the electrode (letters) and contact number (figures). All electrodes were inserted perpendicular to the cortical surface and numbered medial to lateral (i.e. 1 and 2 lie deepest and 12-13 nearest the surface). a. shows a typical seizure in the same patient which propagates from mesial prefrontal/orbito frontal cortex to lateral frontal regions. B. Illustration of the results of identified subsets of co-activated structures in the interictal data (grey lines illustrated correlated regions). Electrodes (medial/lateral contacts): Right orthogonal: OR = orbito-frontal anterior/orbito-frontal lateral, OF = Anterior cingulate/dorso-lateral prefrontal, SA = supplementary motor/pre-motor, A = mesial temporal, OP = insula/ operculum, Right oblique: FR = pre-frontal (medial)/orbitofrontal, PM = thalamus/dorsal premotor cortex, Left: OF’ = anterior cingulate/dorso-lateral prefrontal (left)
2. icEEG direction index at seizure onset

Of the 4 patients who underwent sEEG, the direction index for epileptiform discharges at seizure onset was in agreement with the results of the fMRI DCM analysis for co-localised electrodes in 3 cases. In the remaining case (case 3), the icEEG distinguish a driving region of the 2 identified.

Figure 8-7 Screenshot showing example of calculation of directionality index from icEEG

20 second epoch during a seizure in patient 1. a. Non-linear correlation between sEEG signals recorded at orbito frontal cortex (dashed line) and lateral premotor cortex (solid line). Note increase over first few seconds b. Direction index calculated over the 20 second period (lower trace corresponds to orbito-frontal cortex and is the leading region). Arrow = time of seizure onset on sEEG, x: time (seconds)

3. icEEG Seizure propagation

Comparison of fMRI DCM with seizure propagation on icEEG showed that the model favoured by DCM matched the pattern of seizure propagation in 5/6 patients. In the remaining patient (patient 6) analysis of EEG-fMRI using DCM suggested 2 equally likely models.
8.4.5 Comparison of increased numbers of models

In case 1, I specified 14 models by specifying IEDs as driving or modulatory input on each of the two cortical nodes and specifying either uni or bidirectional couplings between nodes within the network, to explore the data. The right pre-frontal cortex was specified as the 'driving input of the network in this set of models. The comparison of 14 models showed similar results to the simple 3 model comparison approach presented above, with the data best explained by driving input of the IEDs on the orbito-frontal cortex and bidirectional coupling of the all areas within the network. The most likely model was model 4 (relative Log-evidence = 15.67), which considers the IED to have both driving and modulatory input on the model, although this was not significantly different from the several other models in which bidirectional couplings were specified (Models 3-8 specified bidirectional couplings between cortical and sub-cortical structures, while models 1,2 and 9-14 specified unidirectional couplings) (Figure 8-8).
R pre-frontal/orbito-frontal cortex is considered the driver of the model as in the first experiment. The evidence is strongest for model 4, which specified the ‘driver’ of the network as pre-frontal cortex, IEDs as both driving and modulatory input, and bidirectional couplings between all nodes within the network, but the difference in log evidence is not significant when compared with models 3-6 which all specified bidirectional couplings between the thalamus and both cortical regions of the network. The evidence for models 3-6 is more than for any of the models in which only unidirectional couplings were specified. The bottom figure shows the posterior probability of each model being the given the data (for this family of models only).
A further 14 models were made with IEDs specified as input to the lateral premotor cortex, and no model in this group was significantly more likely when the log evidence was calculated. All 28 models were compared in two ‘families’, each including the 14 models specified for the relevant region of interest (similar to a previous study of ictal data (Murta, Leal et al. 2012)).

The best evidence was for the ‘family’ in which the pre-frontal/orbito-frontal cortex was defined as the ‘driver’ of the network (posterior probability 0.82), in agreement with both the previous DCM experiment and the ictal icEEG data.

8.5 Discussion

8.5.1 Main findings:

This is the first attempt to validate fMRI DCM by comparison with icEEG propagation analysis in both interictal and ictal data in humans with epilepsy. It builds on evidence from animal models and a previous study in generalised epilepsy, which suggest that fMRI-DCM, with its incorporated hidden neuronal states may be an appropriate method of non-invasive study of epileptogenic networks over the whole brain.

The findings demonstrate that in 5/6 cases, model selection using DCM on interictal EEG-fMRI data using IEDs as a driving input on different nodes within the epileptic network was in agreement with the pattern of propagation of abnormal neuronal activity during seizures recorded from the same locations on icEEG. In the remaining case the DCM analysis showed significantly greater evidence for two models compared with a third, but there was no significant difference in log evidence between the two (case 6).
In addition, the results of DCM analysis were also in agreement with previously validated models of neuronal coupling in early ictal and interictal activity recorded on icEEG (Wendling, Bartolomei et al. 2001, Bettus, Ranjeva et al. 2011) in 3 out of 4 cases. In the remaining case, it was not possible to identify a ‘driving region’ using the non-linear correlation approach to EEG analysis.

The results of a secondary analysis in a single case (case 1) were in agreement with the previous experiment (identifying the same region as ‘driving the network’) and when an increased number of models were considered, the strongest evidence was for the most complex of models with bidirectional cortico-sub-cortical coupling and IEDs modulating the connectivity in the network in addition to having a direct effect.

8.5.2 Neurophysiological Significance:

The study suggests that fMRI-DCM is a valid approach to the study of the epileptic network and it is able to identify causal relationships between regions which give rise to epileptiform activity. The fact that there was a high degree of concordance between DCM of IED-related fMRI and ictal patterns on EEG is interesting as it suggests that it may be possible to infer information about the dynamics of the epileptic network in seizures from an interictal study, but it is of note the analysis of icEEG data in this study was restricted to activity at seizure onset. While this is a particularly interesting part of the seizure, particularly in the context of pre-surgical evaluation, evidence from both icEEG and optical imaging demonstrate that the coupling in seizures is dynamic and there is evolution in inter-regional connectivity over the course of the event (Wendling, Bartolomei et al. 2001, Wendling, Bartolomei et al. 2003).

In one case (#6), fMRI-DCM showed that one of two models was equally likely. In this case, the two possible ‘driving regions’ in the network were anatomically close and the
irritative zone was very extensive, with frequent synchronised spikes occurring over a large area of cortex encompassing both regions of interest. One possible explanation for insensitivity of DCM to the two different models is that the two regions of interest were very close and resulted from the analysis of large IEDs, which may well relate to a large region of synchronously firing cortex on the icEEG (i.e. I chose ROIs in which the neuronal substrate in each region was not adequately separated). A further possibility is that the model is over-simplistic in this case, and it would be useful to explore this further using a more complex model such as the Bayesian Model Comparison used in case 1.

The patient in whom a ‘driving region’ was not identified on icEEG, differed from the rest of the group as he had prolonged clusters of repetitive right foot jerking and paraesthesia (epilepsia partialis continua), and I hypothesise that although these were associated with rhythmic spiking, there was no increased icEEG coupling associated with seizure onset within the network, (reported in the studies of temporal lobe epilepsy (Wendling, Bartolomei et al. 2001)) and so the inter-regional dynamics were more static on icEEG.

The observation presented here, that fMRI DCM was able to distinguish a single node ‘driving’ the network in all but one case and that the node was found to be concordant with the site of seizure onset rather than propagation adds weight to existing evidence that neuronal models incorporated in DCM-fMRI are applicable to epileptic activity (David, Guillemain et al. 2008, Hamandi, Powell et al. 2008, Vaudano, Laufs et al. 2009, Vaudano, Carmichael et al. 2012) as well as neuronal populations in cognitive networks for which it was developed. This is promising and has implications for further, non-invasive study, both of epileptic networks alone, and their interaction with other networks in the brain.
The observation that more complex models with bidirectional coupling and IEDs modulating the network explained the data better than models with unidirectional coupling, adds to existing evidence that the dynamics of the epileptic network are highly complex and that there is altered connectivity within the irritative zone, although evidence suggests that functional connectivity measured with fMRI is decreased within the epileptic network (Morgan, Gore et al. 2010, Bettus, Ranjeva et al. 2011). I have not investigated specific excitatory or inhibitory effects within the network. As mentioned above, however, the patient had very frequent spikes with frequent bilateral synchrony, despite having a right frontal focus, and I have not investigated the coupling further in the other 5 patients who had more focal abnormalities. It would be interesting to investigate whether this feature is common to patients with fewer discharges and less synchrony.

8.5.3 Methodological and Physiological Considerations

8.5.3.1 Specification of Regions of Interest

DCM relies on the specification of physiologically plausible hypotheses and appropriate selection of ROIs as failure to do this can result in selection of a ‘false model’ (Stephan, Harrison et al. 2007). In cognitive networks, ROIs are well described, but this can be more challenging in epilepsy, where both structural and functional connectivity may be altered. I have addressed this by selecting ROIs of significant IED-related BOLD signal change which are colocalised with electrodes in the irritative zone and the use of identification of coactivated structures on icEEG, in order to ensure that those structures included in the analysis are part of the same (albeit pathological) network in each case. Nevertheless the sampling mismatch between fMRI and icEEG means that there are areas which are not covered by one or other modality which are
not considered in the network. It would be interesting, for example to evaluate the relationship between regions known to be involved in the epileptic network which are not covered by icEEG (for example sub-cortical structures or the precuneus which was suggested by a study in generalized spike and wave discharges to have a gating effect on the corticothalamic network (Vaudano, Laufs et al. 2009).

This is results in a necessary simplification common to all DCM, in which there is a compromise between specifying an accurate model and increasing complexity to the point where data and interpretation becomes unmanageable.

8.5.3.2 Specification of connections

Evidence from previous studies of DCM in epilepsy (Hamandi, Powell et al. 2008) together with animal models of generalised spike and wave activity (Avoli and Gloor 1982) and studies of icEEG in focal seizures (Wendling, Chauvel et al. 2010, Bettus, Ranjeva et al. 2011) suggest that the assumption that bidirectional coupling between nodes within the epileptic network is physiologically plausible. Nevertheless, following the initial validation, I aimed to investigate whether it was possible to improve the specification of the model by testing the two most physiologically plausible hypotheses in a single case with different combinations of uni and bidirectional couplings as well as including the effect of epileptic activity on connectivity within the epileptic network.

This exploratory approach highlighted the problem of comparing multiple models – 1. The number of models becomes more difficult computational perspective if all models are considered and 2. The difference evidence for one model over another becomes small, a problem that could be addressed by further analysis of ‘families’ of models to interrogate specific hypotheses as has been shown in a single case with ictal data, as
well as new DCM methodology designed to address the issues of increased models
(Friston, Li et al. 2011)

8.5.3.3 Suitability of DCM for EEG-fMRI

It should be born in mind that the neuronal model developed for DCM is based on
observations from normal neuronal activity (i.e. local field potential - vascular
coupling)(Friston, Harrison et al. 2003) rather than on IEDs recorded on the scalp,
which do not necessarily behave in the same way. In particular, in this experiment
IEDs are assumed to act directly on the regions and/or connections specified in the
network despite being intrinsically generated rather than arising from an external
source. I have assumed, in common with the previous experiments, that assumptions
made for both the use of the canonical HRF in the GLM and also those underlying
DCM for neuronal networks in healthy subjects hold true for IEDs. A recent
investigation into the relationship between information contained in the EEG and fMRI
data in addition to data investigating non-canonical responses in epilepsy suggest that
the assumption regarding the HRF is valid (Lemieux, Laufs et al. 2008, Rosa, Kilner et
al. 2010, Daunizeau, Lemieux et al. 2012). The DCM approach has been shown to be
applicable to epileptic activity in simultaneously acquired EEG-fMRI in human absence
epilepsy for which there are very robust neurophysiological models (Daunizeau, Lemieux
et al. 2012). The successful recording of simultaneous icEEG-fMRI will enable further
investigation into the coupling of EEG features and haemodynamic changes
(Vulliemoz, Carmichael et al. 2011) (Carmichael, Vulliemoz et al. 2012) (Chaudhary

A recent study evaluating new methodology in DCM has demonstrated that the slow
fluctuations in fMRI data are linked with high frequency EEG data and given that high
frequency activity appears to be highly specific to epileptic networks (Jacobs, Levan et al. 2009) (although the activity is pathological in this case), this suggests newer methodologies may be better able to evaluate these networks. Studies of fMRI correlates of high frequency epileptic activity (e.g. high frequency oscillations and seizure activity) are likely to be possible in the very near future with the evolution of icEEG-fMRI (Carmichael 2013).

8.5.3.4 Yield of EEG-fMRI

In common with the other experiments presented here, the number of datasets in which the method was applied was limited by spike frequency, the occurrence of events within the scanning time.

In addition to this, subjects were only suitable for DCM analysis when multiple regions of highly significant BOLD signal change (withstanding family wise error correction, p<0.05) were identified. New methodology developed by Grouiller et al in collaboration with our group (Grouiller, Thornton et al. 2011) has resulted in improvement in the yield of EEG-fMRI for conventional GLM analysis, but further investigation is required to assess the suitability of this method for DCM analysis as (specifically whether the voltage maps used as input to the GLM are a valid driving or modulatory input for DCM).

8.5.3.5 Asynchronous studies

In common with the other experiments in this thesis, the data presented here was acquired non-simultaneously. In this experiment, this was complicated by the fact that in order to infer network dynamics, we had to assume that the events observed on scalp EEG-fMRI were representative of those arising from those regions in the irritative
zone recorded on icEEG. An additional limitation alluded to above, is that the study only compared IED-related fMRI quantitatively to activity seen at the beginning of the seizure, rather than the entire event. Our observation of seizure propagation allowed a qualitative assessment of the whole event however.

8.5.4 Comparison with existing studies:

The study of both structural and functional connectivity within cognitive networks in epilepsy has revealed differences in frontal lobe, temporal lobe and generalized epilepsy when each group is compared with healthy controls [Vulliemoz et al. 2011] [Voets et al. 2009] [Waites et al. 2006] and others and a comprehensive review of these studies can be found in (Lemieux, Daunizeau et al. 2011).

More recently there has been interest in using fMRI to evaluate the dynamics within the epileptic network using fMR. Bettus et al examined functional connectivity using icEEG and fMRI in patients with focal epilepsy and while icEEG showed higher connectivity between regions affected by IEDs, while there was altered, but lower functional connectivity when the same regions were assessed with fMRI (Bettus, Ranjeva et al. 2011), illustrating that these regions have altered neuronal interactions. They also demonstrated a causal influence between regions within the epileptic network and those which lie outside it. Although the results presented here investigate effective connectivity within the epileptic network, I have not evaluated the influence of the network on other regions in the brain. Recent work within our own group has demonstrated that various methods of analyzing fMRI can also be used to evaluate the interaction between epileptic and cognitive networks (Chaudhary, Centeno et al. 2012, Vaudano, Carmichael et al. 2012).
The use of dynamic causal modeling to evaluate epileptic networks allowing inference of causal relationships is a new and important area of research and although further work is required, the data presented here is an important step in validating the approach and adds to existing studies which have shown that the method is likely to add to our understanding of connectivity within these networks both in focal and generalized epilepsy (David, Guillemain et al. 2008, Vaudano, Laufs et al. 2009, Vaudano, Carmichael et al. 2012).

8.5.5 Clinical significance

Although interesting insights into the neurobiology of epileptic networks can be gleaned from this type of analysis, one of the most important questions remains its clinical relevance to the patients studied. One group has attempted to take the study of connectivity further and has looked at the relationship between functional connectivity in epileptic networks and surgical outcome, noting that when connectivity from IED-related BOLD signal change concordant with the seizure onset zone (SOZ) is lateralized, surgical outcome is more favourable than when it is not (perhaps reflecting a more extensive, and ‘embedded’ epileptic network) (Negishi, Martuzzi et al. 2011).

Two case reports of the use of DCM in focal epilepsy, one applied to interictal data and the second to a seizure recorded with EEG-fMRI, both reported that it was possible to infer patterns of ictal propagation within the epileptic network and the preliminary data presented here is in agreement with this (Hamandi, Powell et al. 2008, Murta, Leal et al. 2012). In the first of these studies, DCM was combined with diffusion tensor imaging allowing the simultaneous assessment of both functional and structural connections. Meanwhile Murta et al have recently demonstrated, in a patient with a hypothalamic hamartoma, that DCM was able to predict seizure propagation, by comparing multiple
families of models including those with unilateral and bilateral connections rather than two hypotheses as has been done here.

The results presented here suggest some validity for DCM in IED-related fMRI at the level of the individual patient rather than a group effect, which although more powerful, is very difficult to study in such a heterogeneous population.

8.5.6 Future directions

A natural extension of this preliminary work, in the first instance is to refine the DCM approach by increasing the complexity and number of models tested using Bayesian Model Comparison to test more ‘families’ of models (Murta, Leal et al. 2012) or stochastic DCM (Daunizeau, Lemieux et al. 2012), following the exploration of the data applied in case 1. In particular, testing of groups of models may be more successful in identifying patterns of connectivity within the network. A further extension of this would be to compare patterns of coupling in interictal and ictal data.

In addition, longitudinal studies assessing how the functional and effective connectivity both within and outside the epileptic network evolves over time might provide further insight into the evolution of the disease and potential treatment outcome.

More recent studies of the epileptic network using icEEG are now focusing on the detection and analysis of ‘high frequency oscillations’ (HFOs) which appear to be one of the signatures of regions within the epileptogenic zone (Jacobs, Levan et al. 2009, Jacobs, Zijlmans et al. 2010) and are probably more specific to the epileptic network than interictal spikes. To improve the validation, it would be interesting to compare the EEG-fMRI data with correlated networks of HFOs in interictal data.
8.6 Conclusion:

In this experiment the results demonstrate that interictal fMRI DCM is able to predict patterns of seizure propagation on icEEG in a small group of patients with focal epilepsy. This opens a new avenue for the non-invasive investigation of epileptic networks and future work may include the evaluation of those regions which are not directly involved in the epileptic network.
EXPERIMENT 5: INTRACRANIAL EEG-FMRI REVEALS CHANGES IN THE EPILEPTIC NETWORK ASSOCIATED WITH SUB-CLINICAL SEIZURES.

9.1 Summary

Background and Aim

Towards the end of the experimental intracranial EEG during fMRI scanning was successfully recorded in a small number of patients. As has been discussed above, the approach to modeling seizures with fMRI is complicated as scalp EEG does not always provide an accurate representation of ictal events on which to model the fMRI response. In addition motion often complicates the interpretation of this data. In a single patient with left hippocampal sclerosis and seizures arising from both temporal lobes, I was able to record a sub-clinical temporal lobe seizure and in this section I aimed to assess whether it was possible to model BOLD signal changes related to the seizure activity.

Methods:

The patient was selected from a series who underwent scalp EEG-fMRI at 3T while awaiting evaluation with intracranial EEG (icEEG). Following investigation with icEEG the patients underwent EEG-fMRI at 1.5T with intracranial depth electrodes in situ. Interictal and ictal events were marked by observers and the ictal event divide into three phases. and interictal and ictal associated haeodynamic change was modeled in SPM8. The resulting maps of haemodynamic change were overlaid on the individuals T1 weighted MRI scan. Regions of BOLD signal change were compared with the epileptogenic zone and irritative zone and regions outside of the EZ were also noted. Results were compared with findings on scalp EEG-fMRI in addition.
Results:

Scalp EEG-fMRI revealed IED associated BOLD signal in the left posterior temporal lobe. icEEG-fMRI revealed small, non-significant clusters of BOLD signal change in both mesial temporal lobe structures and remote from the seizure onset zone associated with right mesial temporal spikes. BOLD signal change associated with the fast activity seen at seizure onset in the right amygdala was seen in the right mesial temporal lobe and remote regions were observed in the default mode network. These differed from the patterns associated with right amygdala/hippocampal IEDs.

Conclusion:

Intracranial EEG-fMRI is able to demonstrate BOLD Signal change concordant with the seizure onset zone. BOLD signal change specific to the early ictal change is seen within the seizure onset zone and is different from the patterns observed with IEDs, either on depth electrodes or at the surface. I hypothesise that these changes represent greater recruitment of the epileptic network compared with interictal discharges.

9.2 Introduction

The mechanisms of ictogenesis (generation of seizures) continues to be the subject of much investigation in epilepsy. Evidence from studies in both human and animal models have demonstrated that epilepsy is an abnormal physiological state during which increased neuronal synchronisation (Zhao, Ma et al. 2009) places demands on cerebral autoregulation, resulting in increased local neuronal oxygen metabolism in the epileptogenic zone. The mechanisms underlying this effect have been studies both in
vitro and to some extent in animal models [Zhao et al. 2007] demonstrating focal changes in perfusion and cerebral oxygenation.

Simultaneous EEG-fMRI has been used to study the haemodynamic associations with both interictal, and more recently ictal activity in patients with focal epilepsy. In around 50% of patients interictal discharge (IED) associated BOLD signal change is observed colocalised with the seizure onset zone (SOZ) [Salek-Haddadi et al. 2006; Al Asmi et al. 2003], while remote clusters are also observed which are often colocalised with regions to which IEDs or seizures propagate [Vulliemoz et al. 2009; Thornton et al. 2011]. Changes are also seen associated with spikes in the so called ‘default mode network’ [Laufs et al. 2006; Aghakhani et al. 2006].

Seizures, which may be manifest on scalp EEG only after the onset, are typically more difficult to model, and the interpretation of seizure associated fMRI changes may also be complicated by confounding factors such as movement. In a previous study which compared these BOLD signal changes with intracranial EEG (icEEG), I found that changes within the seizure onset zone were seen when the scalp EEG accurately reflected the changes seen on icEEG (i.e. there is no lag between icEEG and scalp EEG onset). See Chapter 7 (Thornton, Rodionov et al. 2010). Several series of ictal EEG-fMRI have explored BOLD signal changes both at and prior to seizure onset and demonstrated widespread increase in BOLD signal [Tyvaert et al. 2009; Donaire et al. 2009; Salek-Haddadi et al. 2002; Kobayashi et al. 2006] (Chaudhary, Carmichael et al. 2012) including clusters which co-localised with the seizure onset zone.

A new and exciting development in this field has been the first report of simultaneous intracranial EEG-fMRI, allowing the detailed evaluation of fMRI correlates of neuronal activity [Vulliemoz et al. 2011] (Cunningham, Goodyear et al. 2012). Initial reports of
this technique, demonstrated BOLD signal change correlated with interictal discharges recorded during icEEG-fMRI. Here we report a case in which a patient had an electrographic seizure, allowing the direct investigation of BOLD correlate of seizure activity, without contamination by movement.

9.3 Methods:

9.3.1 Patient selection:

The patient was taken from a consecutive series of patients undergoing icEEG as part of pre-surgical evaluation for drug resistant focal epilepsy at the National Hospital for Neurology and Neurosurgery. Patients underwent scalp EEG-fMRI prior to implantation in addition to standard pre-surgical evaluation including long term video EEG monitoring (LTM), MRI at 3T, neuropsychological assessment and neuropsychiatric assessment. As described in Chapter 3, patients who had no contra-indications and gave consent, were recruited for additional study during the icEEG recording with icEEG-fMRI. Six patients underwent icEEG-fMRI (reported as part of a larger series elsewhere (Chaudhary 2013)), of whom only one had a seizure during scanning. All patients gave informed written consent (sample consent forms can be found in Appendix A).

9.3.2 Scalp EEG-fMRI:

The patient underwent scalp EEG-fMRI at the Epilepsy Centre MRI unit, Chalfont St Peter, using a commercial 64-channel EEG system (BrainProducts, Munich, Germany) and 3Tesla MRI scanner (Symphony, GE, Milwaukee, USA). Further details of the scalp EEG-fMRI protocol have been alluded to in the General Methods section in Chapter 3.1.4.-3.1.9.
9.3.3 icEEG-fMRI Acquisition:

Full details of the icEEG-fMRI protocol are available in our recent publications (Vulliemoz, Carmichael et al. 2011, Carmichael, Vulliemoz et al. 2012). A short summary follows below.

Following completion of the diagnostic icEEG and prior to removal of the icEEG electrodes, the cables were exposed, bundled, rerouted to the vertex and then rebandaged. The cables connecting the electrodes to the amplifiers for the clinical recordings were replaced by shorter cables (length 90 cm) to minimize radio-frequency induced risk of heating and laid out precisely in relation to the scanner [Carmichael et al. 2008] and [Carmichael et al. 2010]. EEG was recorded using an MR-compatible amplifier system (Brain Products, Munich, Germany) and dedicated recording software (Brain Vision Recorder).

MRI was performed using a 1.5 T Siemens Avanto scanner (Siemens, Erlangen, Germany). To limit heating, a head transmit and receive RF coil was used along with low SAR (specific absorption rate) sequences (≤ 0.1 W/kg, head average), as described elsewhere (Carmichael, Thornton et al. 2008, Carmichael, Thornton et al. 2010). The following scans were performed: 1) localiser, 2) FLASH T1-volume (TR 3 s/TE 40 ms/flip angle 90°), 3) two 10-minute gradient echo EPI fMRI scans (TR 3 s/TE 78 ms/ 38 slices/200 volumes, 3 × 3 × 3 mm), during which intracranial EEG was recorded. The patient was asked to lie still with eyes closed and no instruction regarding vigilance was given. The patient and their EEG were monitored by a physician (myself for this experiment) throughout the procedure.

The EEG recording system sampling at 5000 Hz was synchronised to the scanner's 20 kHz gradient clock.
9.3.4 Preprocessing and labeling of events:

9.3.4.1 icEEG

Scanner and pulse related artifact was used using template subtraction methods implemented in Brain Products software and described elsewhere [Allen et al. 2000; Allen et al. 1998]. IEDs were labeled by two observers (RT/UC). We divided IEDs on the basis of localisation of the event and event type. Seizure activity was identified and labeled as a single block with onset and offset time. In addition, seizures were divided into blocks where there was a clear change in activity type (repetitive spikes, fast activity, post ictal slowing), to allow examination of specific haemodynamic changes associated with evolution of the seizure.

9.3.4.2 fMRI

fMRI sequences were realigned and smoothed with a kernel of 8mm FWHM. All fMRI analysis was performed using SPM8 software package (www.fil.ion.ucl.ac.uk/SPM) using methodology described in section 8.3.4.

9.3.5 Analysis:

Data were analysed using a general linear model (GLM) in SPM8. IEDs were considered as zero duration events, and a separate set of regressors was created for each type of IED which was convolved with a canonical HRF. The seizure was modeled as a whole and divided into three blocks as described above to create further regressors which were also convolved with the canonical HRF in the same model. Motion and cardiac related effects were also included in the model in the form of 6 realignment parameters and cardiac confounds respectively [Friston et al. 1998; Liston et al. 2006]
9.4 Results:

9.4.1 Clinical details:

The patient was a 28 year old male with habitual seizures since the age of 7 years. He was born prematurely at 36 weeks and had a single febrile convulsion at 18 months. Structural MRI at 3T showed left hippocampal sclerosis. He had frequent (clusters every 2-3 weeks) seizures consisting of epigastric aura followed by automatisms (right and left hand movements and rhythmic non-clonic hand movements (RINCH)) evolving to a hypermotor seizure (spitting and tapping feet).

Scalp EEG recorded during long term monitoring (LTM) showed interictal epileptiform discharges (IEDs) over the left frontal and temporal regions with independent IEDS. Ictal scalp EEG demonstrated rhythmic slowing over the left anterior temporal region around the time of onset, but this was not always time-locked to clinical onset.

Intracranial EEG (icEEG) was undertaken, as the clinical semiology was not clearly lateralising and the ictal onset on scalp EEG was not clear raising the possibility of non-concordant electro-clinical localization.
9.4.2 Details of icEEG

The Intracranial EEG implantation consisted of 5 depth electrodes with 6 contacts on each as follows:

Table 9.1 Table showing the locations of each depth electrode. Electrode contacts are labelled 1-6, mesial to lateral. Electrode contacts are referred to in later figures by the same labels.

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA 1-6</td>
<td>Left Amygdala</td>
</tr>
<tr>
<td>LHA 1-6</td>
<td>Left anterior hippocampus</td>
</tr>
<tr>
<td>LHP 1-6</td>
<td>Left posterior hippocampus</td>
</tr>
<tr>
<td>RA 1-6</td>
<td>Right amygdale</td>
</tr>
<tr>
<td>RH 1-6</td>
<td>Right anterior hippocampus</td>
</tr>
</tbody>
</table>

Figure 9-1 T1-weighted MRI with intracranial electrodes in situ

IcEEG was recorded over a period of 3 days during which 5 clinical seizure and multiple electrographic seizures were recorded.
Interictal icEEG:

Frequent spikes and polyspikes were recorded from the right amygdala (most frequent), left anterior hippocampus and left posterior hippocampus, with less frequent spikes recorded from the right hippocampus.

**Figure 9-2** Typical intracranial EEG recording showing interictal discharges from right and left hippocampi and amygdale

Seizures:

1. Clinical semiology is as described above. IcEEG showed fast activity and repetitive spikes arising from LA 1-3 spreading to LP 1-3 (Figure 9-3).
Figure 9-3 Typical clinical seizure arising from the left hippocampus. Arrow indicates fast, low amplitude activity at onset.

Electrographic seizures consisting of a build up of fast activity in the right amygdale (RA2) preceded by repetitive spiking in the right amygdale (RA2-3). No obvious clinical change was observed during these events (Figure 9-4).

Figure 9-4. Example of typical sub-clinical seizure arising from the right amygdala.
9.4.3 Scalp EEG-fMRI:

Left temporal sharp waves were recorded during scalp EEG with no independent right sided activity. IED-related BOLD signal change was observed in the left posterior part of the superior temporal gyrus. No ictal events were recorded.

Figure 9-5 Results of Scalp EEG-fMRI.

SPM(F) of IED-related BOLD signal change overlaid on individual EPI. Crosshair at global maximum z= 5.4, p<0.001 uncorrected for multiple comparisons.
9.4.4 Intracranial EEG-fMRI- event based analysis:

Three types of interictal discharge were recorded and 2 electrographic seizures, both arising from the right amygdala were recorded. IED related BOLD signal change is shown below:

Table 9.2 IED related BOLD signal change recorded during icEEG-fMRI

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>BOLD-signal change</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA spikes</td>
<td>41</td>
<td>Null</td>
<td>None</td>
</tr>
<tr>
<td>RA polyspikes</td>
<td>24</td>
<td>R Post Hippocampus</td>
<td>ROF</td>
</tr>
<tr>
<td>LH spikes</td>
<td>29</td>
<td>Null</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 9.3 BOLD signal change associated with electrographic seizures arising from the right amygdala in icEEG-fMRI

<table>
<thead>
<tr>
<th>Event modeled</th>
<th>BOLD signal increase</th>
<th>BOLD signal decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire seizure</td>
<td>Right posterior hippocampus</td>
<td>Right temporal pole</td>
</tr>
<tr>
<td>Early</td>
<td>Right posterior hippocampus</td>
<td>Diffuse regions</td>
</tr>
<tr>
<td>Middle</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Late</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Figure 9-6 Seizure related BOLD signal change recorded with icEEG-fMRI

(Seizure modeled as a single block, crosshair indicates global maximum. SPM(F), z = 7.1, p<0.001 uncorrected for multiple comparisons. Increased BOLD signal change overlaid on hires EPI with electrodes in situ. Medial parietal region of BOLD signal change, not visible on this view, was also seen.)
9.4.5 Resection and progress

Following icEEG, all clinical seizures were identified as arising from the left hippocampus, but additional electrographic seizures appeared to arise from the right hippocampus. Given that neuropsychometry suggested relative preservation of non-dominant function, the option of left anterior temporal lobe resection was discussed with the patient with the aim of reducing the number of seizures and preserving non-dominant temporal lobe function. The patient underwent left temporal lobe resection, with a reduced number of seizures at 6 months and seizure freedom (ILAE class 1) at 36 months. Histology of the resected tissue confirmed hippocampal sclerosis with tissue necrosis around the site of intracranial electrode implantation in keeping with icEEG electrodes.

9.5 Discussion

This is the first reported case in which it has been possible to examine the haemodynamic correlates of ictal activity recorded using intracranial EEG. We were able to show that a localized seizure related BOLD signal change can be seen within the seizure onset zone, and further more that remote effects within regions of the default mode network area are also seen, which are specific to activity seen at seizure onset.

9.5.1 Neurophysiological significance:

9.5.1.1 BOLD correlates of fast activity in the seizure onset zone

Low voltage fast activity has long been recognized as the hallmark of seizure onset recorded using standard macroelectrodes- increase in ‘beta-gamma power’ has
consistently been reported as a marker of the epileptogenic zone at seizure onset both in temporal and extratemporal lobe epilepsy [Bartolomei et al. 1999; Wendling et al. 2003]. The role of this increase in ‘fast’ activity has been the subject of debate and recently it has been hypothesized that increased synchronization through inhibition is necessary for the generation of this fast activity [de Curtis and Gnatkovsky 2009], and the relationship between inhibitory and excitatory neuronal activity at seizure onset is still poorly understood. Evidence from optical imaging in humans demonstrates a dip in HbO2 despite an increase in perfusion suggesting a massive increase in oxygen metabolism occurring in advance of seizure onset [Zhao, Suh, Ma, Perry, Geneslaw, and Schwartz 2007]. The observation, here, increased focal fast activity at seizure onset is associated with and increase in BOLD signal change at the seizure onset, but also changes within remote neuronal networks, suggests these changes in metabolic demand may relate to the increased synchronicity reflected by increased gamma power on the icEEG recording.

An extension to this work is currently being undertaken in our group to investigate whether there are BOLD correlates to specific frequencies on intracranial EEG (similar to that reported by our own and other groups investigating haemodynamic correlates of scalp EEG power spectra (Laufs, Kleinschmidt et al. 2003, Mantini, Perrucci et al. 2007, Tyvaert, Levan et al. 2008).

9.5.2 Changes in the default mode network

The observation that there is a concomitant decrease in BOLD signal change within the ‘default mode network’ supports evidence from intracranial EEG, which demonstrates that the loss of awareness seen in temporal lobe seizures is associated with increased hippocampus-precuneus coupling. In this study changes were only in part of the
default mode network (precuneus) and only at low levels of significance, but it is interesting that although previous studies have demonstrated changes in the default mode network associated with IEDs in TLE at the group level (Kobayashi, Bagshaw et al. 2006, Laufs, Hamandi et al. 2007) changes associated with IEDs were not seen in this case, but only with seizure onset. A possible explanation for this is that the population of neurons firing synchronously required to produce a IED on a depth electrode is much smaller than that required to produce the event at the scalp and a larger population, and the downstream changes in the default mode network perhaps only occur with synchronous firing of larger populations of neurons. Further analysis may provide insight into the neurophysiological mechanism underlying this – one approach would be to incorporate amplitude of the spikes in the model to examine if there is variability in the patterns of BOLD signal change with spike amplitude. Alternatively, simultaneous recording of scalp and intracranial EEG within the scanner would provide the opportunity to examine differences in BOLD signal change between IEDs which are or are not propagated to the surface.

9.5.3 Advantages over scalp EEG-fMRI

One of the key limitations of scalp EEG-fMRI, is the model which is derived from an imperfect representation of the neuronal activity, both in terms of sensitivity (the scalp EEG is only sensitive to large volumes of relatively superficial neuronal activity) and also spatial resolution. It can be seen from the icEEG recordings that in this case a large amount of epileptic activity is seen on the icEEG which is not visible on the scalp, particularly in the right hippocampus and amygdala, which may explain why there is no BOLD signal change on the right using a scalp EEG-fMRI model. By contrast in the icEEG-fMRI model, it can be seen that although the right sided seizures had no apparent clinical correlate, deactivation occurred in regions of the default mode
network, suggesting that there is likely to be a sub-clinical suspension of the resting state. This recruitment of the epileptic network associated with sub-clinical seizures suggests the potential for clinical seizures arising from this region in the future, meaning the likelihood of clinical improvement in the long term is reduced. A recent study of temporal lobe seizures has shown that increased synchronicity in parietal and mesial temporal structures is correlated with loss of awareness in temporal lobe seizures; however this case demonstrates that there may be sub-clinical changes in these ‘resting state networks’ associated with electrographic seizure activity even in the absence of a clinical depression of consciousness [Arthuis et al. 2009].

9.6 Conclusion

There is no obvious immediate clinical value in recording simultaneous icEEG-fMRI, but we anticipate that these experiments will inform our understanding of the neurobiology of seizures and their generators, which may have an indirect impact on the management of patients. Moreover the ability to record intracranial EEG in the scanner environment opens avenues for the study of cognitive processing across the whole brain alongside the high temporal and spatial resolution, but limited spatial coverage, within specific structures offered by icEEG.
10 EXPERIMENT 6: RESULTS OF MEDIUM TERM FOLLOW UP IN PATIENTS UNDERGOING PROSPECTIVE STUDY WITH EEG-FMRI

10.1 Summary

Background and Aim:

Following the completion of the studies described above, I sought to evaluate the clinical role of scalp EEG-fMRI by identifying the groups of patients in whom the technique is of most value. Since the completion of the experimental work, there have been several studies which have attempted to compare EEG-fMRI with intracranial EEG, including those presented here and a further evaluation undertaken by our own group in collaboration with a group in Geneva. None of these have, however, attempted to evaluate the role of the technique in an unselected group of patients undergoing icEEG and there is also limited data on post-surgical outcome, particularly beyond 12 months follow up. The final section of the work summarises the findings across the entire cohort and focuses on identifying the group in whom the technique is most likely to add value.

Methods:

Consecutive patients awaiting icEEG for focal epilepsy were recruited from three centres in the UK and one in France. All patients underwent scalp EEG-fMRI as described in chapter 3 alongside standard pre-surgical evaluation. Patients were selected regardless of the number of IEDs on their resting EEG. Data were preprocessed and analysed using an IED based General Linear Model as described in chapter 3 and patterns of BOLD signal change were compared with intracranial EEG.
Studies were classified as ‘localising’ if IED-related BOLD signal change was isolated to one lobe, and ‘non-localising’ if BOLD signal change was widespread or no BOLD signal change was associated with IEDs.

The number of patients who had localizing information on EEG-fMRI and those who had a localizing icEEG were identified Fisher’s exact test was calculated for patients with ex TLE, neocortical TLE and mesial TLE who had IEDs during EEG-fMRI to assess the relationship between patients with a localizing EEG-fMRI study and localizing icEEG. A separate analysis was undertaken for the total number of patients studied including those who did not have IEDs during scanning. I also compared the sensitivity and specificity of a EEG-fMRI for a single seizure focus on icEEG. Finally I compared the EEG-fMRI in patients who had IEDs during scanning with post-operative outcome at 3 years.

Results:

101 consecutive patients were recruited and underwent EEG-fMRI over three years of whom 37 had IEDs during EEG-fMRI with or without seizures. A further 3 patients had seizures only. Of the 37 patients in whom seizures were recorded, 15 had frontal lobe epilepsy, 6 had neocortical temporal lobe epilepsy, 4 had mesial temporal lobe epilepsy, 5 had parietal lobe epilepsy and 3 had occipital lobe epilepsy. In 3 patients it was not possible to localize seizures on the basis of standard electro-clinical localization. BOLD signal change was recorded in 31/35 patients. 21 patients had a ‘localising’ OLD signal change. A localising EEG-fMRI was significantly associated with a ‘localising’ icEEG study in neocortical epilepsy (p= 0.0108), but not if mesial TLE was included in the analysis (p = 0.08). A localizing EEG fMRI was not significantly associated with post-operative outcome.
10.2 Introduction

The work presented in this thesis has sought to address the relationship between the results of EEG-fMRI studies and intracranial EEG and we have demonstrated concordance between IED-related BOLD signal change and icEEG in focal cortical dysplasia as well as demonstrating some relationship between IED-related BOLD signal change and post-operative outcome in a small series of patients with focal epilepsy of mixed aetiology in line with previous and more recent studies of EEG-fMRI (Al-Asmi, Benar et al. 2003, Benar, Grova et al. 2006, Salek-Haddadi, Diehl et al. 2006, Zijlmans, Huiskamp et al. 2007). A heterogeneous group of the patients presented here have also been studied using new methods of EEG-fMRI analysis in which increased concordance with icEEG was demonstrated compared with conventional IED related analysis (Grouiller, Thornton et al. 2011) (Vulliemoz, Thornton et al. 2009, Caballero-Gaudes, Van de Ville et al. 2013), suggesting that sophisticated analysis of EEG data may lead to improvements in the clinical applications of the technique.

A more recent prospective study has compared EEG-fMRI with icEEG in a mixed group of 16 patients with frequent IEDs and reported that IED-associated BOLD signal change co-localised with the seizure onset zone in 83% of patients at a sub-lobar level, although outcome following resection did not appear to relate to whether the region of BOLD signal change included the resection area (van Houdt, de Munck et al.) contributing to the increasing body of evidence that EEG-fMRI may have a role in the planning of pre-surgical evaluation of focal epilepsy, especially icEEG implantation.

Despite these advances, however, a definitive, prospective evaluation of EEG-fMRI is still required. Other novel techniques in pre-surgical evaluation, such as MEG and interictal PET have been systematically compared with intracranial EEG, usually in
patients with inconclusive video EEG monitoring and/or negative structural MRI (Knowlton 2006, Knowlton, Elgavish et al. 2008, Stefan, Rampp et al. 2010).

The final part of this thesis, therefore, in contrast to the detailed case reports presented earlier, attempts to summarise the results obtained during the course of study and to draw some conclusions about the potential clinical utility of the technique in various groups of patients.

10.3 Materials and Methods

10.3.1 Patients

Patients were recruited from four centres and underwent standard electroclinical evaluation at their local centre as well as clinical assessment and structural imaging at the Epilepsy Society MRI Unit as described in chapter 3. Patients were divided into 3 main groups on the basis of standard pre-surgical evaluation; Extra Temporal Lobe Epilepsy (comprising patients with frontal lobe epilepsy, parietal lobe epilepsy, occipital lobe epilepsy and those who has a presumed focal, cortical epilepsy which was not localized at a lobar level), Lateral temporal lobe epilepsy and mesial temporal lobe epilepsy.

10.3.2 EEG-fMRI acquisition and analysis

All patients underwent 40-60 minutes of scalp EEG-fMRI as described in the common methodology section. Data were pre-processed and analysed using the same approach as the previous IED-related EEG-fMRI studies described in chapters 3, 5 and 6 in SPM5.
10.3.3 Comparison with intracranial EEG

Individual IED-related BOLD maps were overlaid on individual T1-weighted MRI scans fused with CT with intracranial electrodes in situ as previously described and the position of each region of IED-associated BOLD signal change noted. Concordance with icEEG was assessed in the same way as previously.

10.3.4 Assessment of localization

10.3.4.1 EEG-fMRI

EEG-fMRI studies were considered to be 'localising' when the clusters of IED-related BOLD signal change were restricted to or bordered on a single lobe (classified C, C+ or D according to our previous classification). Studies in which widespread BOLD signal change (classified D+) or no IED related BOLD signal change were considered to be ‘non-localising’. The labels were applied regardless of whether the cluster identified was concordant with the icEEG localization to avoid a situation where we only compared concordant clusters with the IZ or SOZ. Studies in which no spikes were recorded were considered ‘null’. Following the observation that IED-associated negative BOLD signal change in the default mode network is widely reported in EEG-fMRI experiments and known to be a downstream effect of epileptic activity rather than part of the epileptic network (Archer, Abbott et al. 2003, Hamandi, Salek-Haddadi et al. 2006, Laufs, Hamandi et al. 2007) we also considered studies to be localizing if this was the only region of BOLD signal change other than localized positive BOLD signal change.
10.3.4.2 icEEG

Intracranial EEG studies were considered ‘localising’ where a single seizure onset zone was identified (similar to previous comparisons (Knowlton, Elgavish et al. 2008)). The label was applied regardless of whether the patient proceeded to resection (in some patients, surgical resection was not carried out owing to the risk of functional deficit following surgery). IcEEG was considered ‘widespread’ when a very widespread or multifocal seizure onset zone was found. If no seizures were recorded the icEEG study was considered ‘null’.

10.3.5 Statistical Analysis

In order to analyse the localizing value of EEG-fMRI in each group, I applied Fisher’s exact test ($\chi^2$ allowing for the small numbers under study) to the data, to assess the relationship between EEG-fMRI studies and icEEG. We also calculated sensitivity, specificity and positive and negative predictive values for localizing IED-related BOLD signal change.

10.3.6 Post-operative outcome

Post-operative outcome was assessed at 3 years using the ILAE outcome scale. Outcomes were considered ‘good’ if a patient had a >50% reduction in seizure frequency (ILAE 1-3), and ‘poor’ if there was a >50% reduction in seizure free days or any increase (ILAE 4-6) similar to in the study of Focal cortical dysplasia in chapter 6.
10.4 Results

10.4.1 Patient groups

In total 101 patients were scanned between 2006 and 2010. 99/101 remained in the study; one moved abroad and one died (SUDEP) prior to any further evaluation. Standard pre-surgical evaluation was carried out in all patients and initial localization is summarized below. Total numbers for each group are given by centre followed by the number of patients in whom IEDs were recorded.

**Table 10.1 Numbers of patients who underwent EEG-fMRI.**

<table>
<thead>
<tr>
<th>Centre</th>
<th>Localisation</th>
<th>Ex TLE</th>
<th>LTLE</th>
<th>MTLE</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Frontal Total (IEDs)*</td>
<td>Parietal Total (IEDs)</td>
<td>Occ Total (IEDs)</td>
<td>Non-localised Total (IEDs)</td>
</tr>
<tr>
<td>NHNN</td>
<td></td>
<td>21 (13)</td>
<td>5 (4)</td>
<td>1 (0)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Bristol</td>
<td></td>
<td>3 (0)</td>
<td>1 (0)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Marseille</td>
<td></td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>KCH</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (0)</td>
</tr>
<tr>
<td><strong>All centres</strong></td>
<td><strong>27 (15)</strong></td>
<td><strong>7 (5)</strong></td>
<td><strong>4 (3)</strong></td>
<td><strong>8 (3)</strong></td>
<td><strong>21 (6)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: LTLE lateral temporal lobe epilepsy, MTLE mesial temporal lobe epilepsy ExTLE, Extra temporal lobe epilepsy, Occ occipital. IED interictal epileptiform discharge, NHNN: National Hospital for Neurology and Neurosurgery, London, UK, KCH Kings College Hospital, London UK. *Figure in parentheses indicates number in whom IEDs were recorded.

10.4.2 Type and number of IEDs

Interictal epileptiform discharges were recorded in 37/99 of patients. The mean number of IEDs and proportion of patients in whom IED-related BOLD signal change were recorded are given in Table 10.2. In four patients >1 type of IED were recorded. In one
patient, significant IED-related BOLD clusters were found related to two IED types, in close proximity to one another in the same lobe. In the others significant IED related BOLD signal change only related to one type. All significant results including those uncorrected for multiple comparisons are reported as they were compared with icEEG, but the percentage of patients in each group in whom the result withstood the more stringent statistical test of p<0.05 family wise error corrected for multiple comparisons are recorded.

**Table 10.2 Summary of findings**

<table>
<thead>
<tr>
<th>Epilepsy type</th>
<th>All patients</th>
<th>Patients in whom IEDs were recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% with IED related BOLD signal change</td>
<td>Median no of IEDs in 40 minutes</td>
</tr>
<tr>
<td>ExTLE</td>
<td>FLE</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>PLE</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>OLE</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>NLE</td>
<td>25</td>
</tr>
<tr>
<td>LTLE</td>
<td>LTLE</td>
<td>23</td>
</tr>
<tr>
<td>MTLE</td>
<td>MTLE</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Abbreviations: FLE frontal lobe epilepsy, PLE parietal lobe epilepsy, OLE occipital lobe epilepsy, NLE non-localised neocortical epilepsy, LTLE lateral temporal lobe epilepsy, MTLE mesial temporal lobe epilepsy

**10.4.3 Analysis of patients who had IEDs during recording: comparison with icEEG**

29/37 patients in whom IEDs were recorded proceeded to intracranial EEG. Of the remaining eight, three were offered resection without icEEG, as following further assessment it was felt there was enough information to proceed with resection. In four,
the seizure onset zone was regarded to be too extensive to plan invasive EEG. The remaining patient had highly concordant electro-clinical information, but declined invasive EEG as they did not wish to undergo resection with a risk of functional deficit.

### 10.4.3.1 Relationship between EEG-fMRI and Seizure onset zone

IED-related BOLD signal change defined as ‘localising’ according to the above criteria was found in 21 patients. In the remaining 16 patients the EEG-fMRI was considered non-localising (either widespread BOLD signal change was observed or no IED-related BOLD signal change). I have included eight patients who did not undergo icEEG in this analysis as the same clinically relevant information was available from non-invasive investigations. It should be noted that EEG-fMRI was not used in planning the placement of electrodes.
Table 10.3 Table showing the numbers of patients with localising or non-localising EEG-fMRI and icEEG studies (patients with IEDs during EEG-fMRI)

<table>
<thead>
<tr>
<th></th>
<th>icEEG/non invasive data localized (resection with no icEEG)</th>
<th>icEEG widespread/ SOZ too widespread for invasive EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExTLE EEG-fMRI localized</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>ExTLE EEG-fMRI widespread/null</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>LTLE EEG-fMRI localized</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>LTLE EEG-fMRI widespread/null</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>MTLE EEG-fMRI localized</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MTLE EEG-fMRI widespread/null</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total Neocortical EEG-fMRI localized</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Total Neocortical EEG-fMRI widespread/null</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total EEG-fMRI localized</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Total EEG-fMRI widespread/null</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

icEEG = intracranial EEG, SOZ = seizure onset zone, TLE = temporal lobe epilepsy L = lateral, M = medial.

When EEG-fMRI was defined as ‘localizing’, icEEG was significantly more likely to be localized or the seizure onset zone could be defined without icEEG and if IED-related BOLD signal change was more widespread, icEEG was significantly likely to be widespread in neocortical epilepsy (Fisher’s exact test: p=0.0152 for Extra TLE and p=0.0108 for all neocortical epilepsy).

The relationship was not significant if the results for mesial temporal lobe epilepsy are also considered (p=0.08). I did not calculate the significance level separately for the temporal lobe groups as they are too small for meaningful analysis.
10.4.3.2 Predictive value of EEG-fMRI studies when IEDs are recorded

The sensitivity and specificity of localized, concordant (i.e. classified C or C+ using our previous system) IED-related BOLD signal change for a localized icEEG focus in patients who have IEDs on EEG-fMRI and underwent icEEG

Table 10.4 Predictive value of localized IED-related BOLD signal change on EEG-fMRI for a single icEEG focus

<table>
<thead>
<tr>
<th></th>
<th>Ex-TLE (95% CI)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>78.9 (53.9-93.0)</td>
<td>69.6 (46.9-85.9)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>69.2 (38.8-93.6)</td>
<td>64.29 (35.6-86.6)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>79 (53.9-93.0)</td>
<td>76.2 (52.4-90.8)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>69.23 (38.8-89.6)</td>
<td>56.25 (30.6-79.2)</td>
</tr>
</tbody>
</table>

PPV= positive predictive value, NPV = negative predictive value, exTLE= extra temporal lobe epilepsy

10.4.4 Analysis of all patients: relationship between EEG-fMRI and icEEG

74/99 patients recruited underwent icEEG. Five were lost to follow up (all with no IEDs). The remaining 20 patients either proceeded to resection without further investigation (n=7) or were declined further investigation (either because the seizure onset zone was felt to be too widespread following non-invasive evaluation for a likely successful outcome or owing to the risk of complications). For the 81 patients who underwent icEEG or had adequate information to proceed to resection, the predictive value of a localized positive region of IED-related BOLD signal change on EEG-fMRI using conventional IED-related general linear model analysis is given below.
Table 10.5 Relationship between localised EEG-fMRI and localised icEEG (figures indicate numbers of patients in each group)

<table>
<thead>
<tr>
<th></th>
<th>Localized icEEG or resection only</th>
<th>Non-localised icEEG/ too widespread to undergo icEEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised EEG-fMRI</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Non-localised EEG-fMRI or no IEDs</td>
<td>32</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 10.6 Specificity/ sensitivity of EEG-fMRI in all patients for single focus on icEEG (including those with no IEDs on EEG-fMRI)

<table>
<thead>
<tr>
<th></th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>34.0 (21.2-49.3)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>85.3 (68.2-94.4)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>76.1 (52.4-90.1)</td>
</tr>
<tr>
<td>NPV</td>
<td>48.3 (35.3-61.4)</td>
</tr>
</tbody>
</table>
10.4.5 Relationship with post-operative outcome at 3 years

Post operative outcome data for the 32/37 patients who had IEDs during EEG-fMRI and underwent resection or in whom icEEG precluded resection is given below (icEEG in 29, resection only in 3). In one patient, the icEEG was non-localising as no seizures were recorded during implantation and in a further patient the seizure onset zone was focal but overlapped with primary motor cortex precluding resection. Data in the remaining 30 patients are summarised in the figure 10-1 and table 10.7.

Figure 10-1 Chart showing the relationship between patients with localising EEG-fMRI and post-operative outcome. (number of patients on y-axis)
Table 10.7: Relationship between extent of EEG-fMRI and post-operative outcome in patients with IEDs (3 years post-operative follow up).

<table>
<thead>
<tr>
<th></th>
<th>ILAE outcome 1-3 (&gt;50% reduction in seizure free days)</th>
<th>ILAE Outcome 4-6 or no resection as icEEG too widespread (up to 50% reduction in seizure free days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised EEG-fMRI</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Non-localised EEG-fMRI</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

The relationship between localizing EEG-fMRI and a good outcome calculated using Fisher’s exact test was not statistically significant (p=0.136)

10.4.6 Patients with no IEDs

45/62 patients with no IEDs during EEG-fMRI underwent icEEG, of whom 28 proceeded to resection and have 3 year follow up data, and the remaining 17 patients did not proceed (either because of inadequately localised seizure onset or a high risk of post operative deficit). Of the 28 patients who underwent resection, 17 had good outcome (ILAE 1-3) and 11 had poor outcome (ILAE 4-6). These figures are comparable with the group who did have IEDs during scanning.

10.5 Discussion

10.5.1 Main findings

In an unselected group of patients with complex focal epilepsy, IEDs suitable for conventional GLM analysis were recorded in 37% of patients. The yield was much lower in patients with mesial temporal lobe epilepsy (12.5%), while IEDs were recorded in 46% of patients with extra temporal lobe epilepsy. Across the whole patient group,
the technique had poor sensitivity for detecting a single region of seizure onset, owing to the low number of patients in whom IEDs were recorded, but positive IED-related BOLD signal change was specific for a single icEEG defined region of seizure onset. This is the largest cohort of patients in whom EEG-fMRI has been compared prospectively with icEEG and more importantly, post-operative outcome and at present the only study with medium term follow up data.

When IEDs were recorded in patients with Extra-temporal lobe epilepsy, positive localized, IED-related BOLD signal change was both sensitive and specific for localizing icEEG, in agreement with smaller case series presented elsewhere ((Zijlmans, Huiskamp et al. 2007, Moeller, Tyvaert et al. 2009, van Houdt, de Munck et al. 2013, Pittau et al 2012)). The technique was both less specific and less sensitive when patients with temporal lobe epilepsy are included, however.

In general, widespread IED-related BOLD signal change was significantly associated with widespread abnormality on icEEG and conversely localized BOLD signal change is significantly associated with localized icEEG at a lobar level.

At 36 months, there is a trend towards better results with regard to a good outcome with regard to seizure frequency with localizing EEG-fMRI compared to a non-localising study in patients with IEDs, in keeping with the pilot data in chapter 5, but the relationship is not statistically significant.

10.5.2 Clinical and neurophysiological Significance

The results presented here are the first formal assessment of the predictive value of EEG-fMRI in an unselected group of patients undergoing icEEG and resection for focal epilepsy and are the largest cohort reported to date to have undergone EEG-fMRI
with robust validation. The finding that when IEDs are recorded, the technique is both sensitive and specific for detection of the seizure onset zone at a lobar level, is encouraging, but the overall low sensitivity of the technique suggests that in its current form it would only benefit a small number of patients and only those in whom very frequent IEDs are recorded. This is something which EEG-fMRI shares with MEG as mentioned in the work looking EEG-fMRI in FCD (chapter 6) as well as interictal PET. When IEDs are recorded however, measures of sensitivity and specificity for the seizure onset zone are better than either interictal PET or SPECT, but not as good as those reported for MEG. Taken alone, the specificity and sensitivity as well as positive predictive value of an isolated region of IED-related BOLD signal change for a single icEEG focus in extra-temporal lobe epilepsy is comparable with results obtained in interictal MEG (Knowlton, Elgavish et al. 2008).

The observation that 8/9 patients who had a very widespread seizure onset zone on icEEG precluding resection also had widespread regions of IED related BOLD signal change reiterates the point made in earlier sections of the thesis, that widespread IED-related BOLD signal change should raise a warning of a ‘failed’ icEEG implantation. Taken together these findings support evidence from smaller series that EEG-fMRI is likely to be most useful in planning or deciding not to pursue icEEG rather than a standalone method of localizing seizure onset.

The comparison with post-operative outcome did not show a statistically significant relationship between localizing EEG-fMRI and good outcome, but there was a trend towards this pattern (figure 10-1). This is similar to findings from a more recent study of 16 patients with pharmacoresistant focal epilepsy (van Houdt, de Munck et al. 2013) which demonstrated that although regions of IED related signal change were included in the resection area in many patients, there was no relationship between the extent of
BOLD signal change and surgical outcome. The mismatch between localizing EEG-fMRI vs icEEG and localizing EEG-fMRI vs post-operative outcome reflects the fact that EEG-fMRI appears to image networks of BOLD reflecting patterns of IED or ictal activity onset and propagation (Salek-Haddadi, Diehl et al. 2006, Groening, Brodbeck et al. 2009, Vulliemoz, Lemieux et al. 2010, Pittau, Dubeau et al. 2012) and therefore we only assessed localization at a lobar level. Increased temporal resolution through the use of ultrafast MRI sequences (Jacobs 2012) or combination with electrical source imaging (Vulliemoz, Lemieux et al. 2010) may improve the specificity of IED-related BOLD signal change for activity onset vs propagation and therefore localization of the seizure onset and irritative zones.

The observation that the technique is less sensitive and specific in mesial TLE than in neocortical epilepsy may relate to the fact that EPI has a high amount of signal drop out in the temporal regions, meaning that it is less sensitive for IED-related BOLD signal change in the temporal lobe.

10.5.2.1 Regions outside the epileptic network

For the purposes of this analysis we did not consider negative BOLD signal change within the default mode network, as this is a recognized finding, widely reported in relation to IEDs and does not contribute to seizure localization. Recent preliminary work with children suggests that the suspension of resting state networks may not be isolated to the default mode network and may depend on task/state at the time of the IEDs (Carmichael 2013). It may be that an independent method to identify these networks would help to increase sensitivity and specificity of the technique, e.g. independent component analysis, effectively treating the resting state network as a physiological confound.
10.5.2.2 Patients with no IED-related BOLD signal change

There were no features specific to those patients in whom IEDs, but no haemodynamic change were recorded. This is a widely reported finding in EEG-fMRI studies and further work is required to evaluate whether there are features common to this group of patients. Following the observations of increased connectivity within the epileptic network, more widely distributed abnormality and poorer outcome with duration of epilepsy in many studies (Aubert, Wendling et al. 2009, Morgan, Rogers et al. 2011), it would be interesting to investigate in future whether there is a relationship between distribution of IED-related BOLD signal change and duration of epilepsy. Similarly in patients with no IEDs at all, there were no specific features and the proportion of patients who underwent resection and outcome data were comparable to the group in whom IEDs were recorded.

10.5.3 Methodological considerations;

In addition to the issues surrounding yield of IEDs and assumptions regarding neurovascular coupling common to both this and the experiments presented in chapters 6 and 7, there are further limitations, which may affect this experiment.

10.5.3.1 Sample size and statistical approach

I used Fisher's exact test to assess the relationship between EEG-fMRI and icEEG as the number of patients in whom IEDs were recorded is very small. The measures of sensitivity and specificity, while apparently good, suffer from low power and have wide confidence intervals. Following this experiment it has been shown in an overlapping group of patients, that an alternative technique for mapping epileptic activity may be able to improve the yield of EEG-fMRI increases yield (Grouiller, Thornton et al. 2011)
and application of this method to the same data may produce more clinically relevant data.

10.6 Conclusions

This is the largest prospective study of EEG-fMRI validated with icEEG and post-operative outcome and the only study, which reports follow up data beyond 12 months. The findings suggest that localised IED-related BOLD is sensitive and specific for the seizure onset zone at a lobar level (although the sample size is small), but is not predictive of post-operative outcome. In addition the data adds to the increasing body of evidence suggesting that widespread IED-related BOLD signal change is associated with poor localization on icEEG and consequently poor outcome.
11 CONCLUSIONS AND CONTEXT

This section aims to summarize the main findings in the thesis and briefly discuss potential implications and possible future directions of the work presented. The overall aim of the work was to look at ways in which a relatively new imaging method could be translated into a clinically relevant technique for planning epilepsy surgery as well as evaluating its potential shortcomings. In addition, I aimed to use various approaches to data analysis to explore the use of EEG-fMRI in the study of epileptic networks and their behavior.

11.1 Summary of main findings

The work presented here represents a proportion of the results of a large multi-centre UK Medical Research Council funded programme which is the first major prospective study comparing EEG-fMRI, intracranial EEG and Post-operative Outcome. One hundred and one patients were recruited to the study, of whom ninety nine were followed up and eighty three proceeded to intracranial EEG.

11.1.1 EEG-fMRI and post operative outcome

In a pilot study with data acquired at both 1.5 and 3 T, I demonstrated that when regions of IED-related BOLD signal were highly focal and concordant with the seizure onset zone (such that surgical resection encompassed the entire region of BOLD signal change), post-operative outcome with regard to seizures, was usually good, while if large regions of BOLD signal change lay outside of the resection margin, poor outcomes were seen.
11.1.2 Non-invasive imaging of epileptic networks in Focal Cortical Dysplasia

This was, to my knowledge, the first reported prospective comparison of EEG-fMRI with intracranial EEG, the gold standard for the investigation of FCD. Regions of IED-related BOLD were concordant with the IZ in the majority of cases, and furthermore, in agreement with the pilot study, in patients where IED-related BOLD signal change was more extensive, surgical outcomes were worse at 1 year. Results demonstrated non-invasive identification of previously unidentified epileptic foci in 2 patients similar to a previous study in an unselected group.

11.1.3 Haemodynamic changes linked to seizures

Nine patients had seizures during the study. General linear model analysis demonstrated significant regions of ictal activity associated BOLD signal change concordant with the seizure onset zone only when the scalp EEG accurately reflected the temporal course of ictal activity. Allowing flexibility in the shape of the haemodynamic response to remove constraints on the way in which the activity was modeled improved results. Independent component analysis refined by the use of a classifier to improve specificity of the components was successful in identifying ‘ictal patterns’ of haemodynamic change in all patients studied.

11.1.4 Electrophysiological networks involved in the generation of seizures: A validation of Dynamic Causal Modeling with intracranial EEG

Six patients who had more than one region of significant IED-related BOLD signal change colocalised with an electrode at which epileptic activity was recorded, were analysed using fMRI-DCM and I was able to demonstrate, using a simple model, that fMRI-DCM predicted patterns of seizure propagation in the epileptic network in 5/6
patients and that in 4 patients who underwent sEEG, a non-linear correlation analysis of the high frequency activity at seizure onset was also in agreement with the results of fMRI-DCM. The application of a more complex model in a single case also fitted with the pattern of seizure propagation in this patient.

11.1.5 Simultaneous intracranial EEG-fMRI of ictal activity

A single patient had a seizure during intracranial EEG-fMRI, which was recorded successfully in its entirety without adverse effects. A general linear model of fast activity in the right amygdala at seizure onset was correlated with BOLD signal change in the right mesial temporal lobe and also within regions of the default mode network, which were not seen in the later phases of the seizure. This activity was more extensive than that seen with IED-related BOLD signal change on icEEG-fMRI either in this patient or in our previous study.

11.1.6 Medium term follow up

I have shown that localising IED-related BOLD signal change is significantly associated with localization on icEEG and conversely, widespread IED-related BOLD signal change is associated with poorly localized seizure onset. There is a general trend towards more widespread EEG-fMRI activations being associated with poorer outcome although this is not statistically significant. The power of the study remains restricted by relatively small sample size, but the figures are comparable with other non-invasive modalities ant the results, nevertheless, represent the first outcome data beyond 12 months and the largest series of EEG-fMRI in pre-surgical evaluation reported to date.
11.2 Methodological considerations

The details of the methodological considerations of each experiment have been discussed in the relevant chapter, but there are some common themes to which more recent developments in the field may add value. At present the methodological developments in EEG-fMRI are evolving extremely rapidly, not only in the study of epilepsy, but also in the study of normal brains (in the resting state and in tasks). An exhaustive discussion of these developments is beyond the scope of this work, but there are several recent comprehensive reviews (Huster, Debener et al. 2012) (Rosa, Daunizeau et al. 2010) and the more relevant issues are highlighted below.

11.2.1 The problem of yield: Approaches to improve sensitivity

The first aim of this work, to evaluate the potential clinical role of EEG-fMRI as a technique to image the seizure onset zone in patients undergoing surgical resection for focal epilepsy, used conventional IED-related GLM analysis and highlighted a problem common to EEG-fMRI, high resolution EEG and MEG, namely the lack of IEDs recorded during scanning (discussed in more detail in the relevant sections above). Various approaches to address this issue could be considered to improve this ranging from patient factors (for example performing recordings following sleep deprivation to increase the proportion of light sleep) to alterations in imaging protocols and EEG analysis.

Following this work, together with external collaborators, this issue has been addressed by focusing on more sophisticated analysis of the EEG using techniques to extracting features other than observer identified IEDs from out of scanner EEG which can then be applied to the EEG recorded during EEG-fMRI (Grouiller, Thornton et al. 2011, Caballero-Gaudes, Van de Ville et al. 2013). Another approach was taken in
interesting recent work which incorporated an EEG transfer function derived from normal subject data (Rosa, Kilner et al. 2010) into the EEG model to improve sensitivity of EEG-fMRI for focal epileptic networks (Leite, Leal et al. 2013). It seems likely that, although the investigation of IED-BOLD signal change has yielded interesting results, future developments are likely to focus on the identification or derivation of other variables EEG, such that measures of 'epileptic activity' rather than IEDs per se are used in modeling haemodynamic effects in epilepsy.

Developments in MRI sequences are also promising for increasing sensitivity for IED-related BOLD (e.g. ultra-fast MRI acquisition (Jacobs 2012) to detect BOLD signal change).

11.2.2 Improving specificity: Refinement of approaches to modeling

The approach to the analysis of fMRI data is to incorporate as much information as possible into any given model resulting in any signal variance attributable to a given effect of interest being highly specific. I have used a fairly conservative approach to modeling haemodynamic changes throughout this work (in common with previous work within our group), by incorporating regressors for motion and pulse artifact to optimize specificity; however, improvements in the specificity and sensitivity of fMRI models remain an active area of research in EEG-fMRI. Recent studies have identified fMRI correlates of other neurophysiological variables such as sleep state or other endogenous brain rhythms (Laufs, Kleinschmidt et al. 2003, Moehring, Moeller et al. 2008, Tyvaert, Levan et al. 2008), eye movements (Chaudhary, Rodionov et al. 2012) which could be incorporated into models to improve sensitivity. Further scope for study would also include the effect of specific anti-epileptic drugs on the results of EEG-fMRI experiments, which I did not control for in this study. The incorporation of these
variables into the modeling of epileptic activity may result in improved specificity and sensitivity of the technique to detect both interictal and ictal haemodynamic changes in future experiments.

The subject of neurovascular coupling and EEG transfer functions in epilepsy remains an active area of research (Carmichael, Hamandi et al. 2008, Rosa, Kilner et al. 2010) both with respect to interictal and ictal data and one of the limitations of the work presented here is that when the experiments were planned, I assumed normal neurovascular coupling in line with previous studies. This has been discussed in more detail in chapter 2 and chapter 6 and is an interesting area to develop the work presented here further, particularly with the advent of icEEG-fMRI recording (Vulliemoz, Carmichael et al. 2011, Cunningham, Goodyear et al. 2012, Chaudhary 2013) which should better inform our understanding of the relationship between events recorded on the scalp, their neuronal correlates and associated haemodynamic changes. Other developments which may increase our understanding of these relationships include the use of near infra-red spectroscopy (Roche-Labarbe, Zaaimi et al. 2010), and oxygen sensitive electrodes (Zhao, Suh et al. 2007, Zhao, Ma et al. 2009) which suggest that the haemodynamic correlates of epileptic activity are more complex than those measured with a constrained HRF in EEG-fMRI.

11.3 Neurobiological and Clinical Context: Future Directions

11.3.1 Ictal EEG-fMRI: Understanding what happens before the seizure

One of the key findings in my study of patients with seizures, was the fact that neither the canonical HRF nor the flexible Fourier model were adequate to detect BOLD signal change concordant with the seizure onset zone in some of the patients. While some of
this can be attributed to movement, my observations from the independent component analysis demonstrated that there were probably changes in haemodynamics before seizure onset. It has been noted above that there are multiple studies which have noted early hemodynamic changes in simultaneous EEG-fMRI recordings of seizures (Federico, Abbott et al. 2005, Donaire, Bargallo et al. 2009, Tyvaert, LeVan et al. 2009, Chaudhary, Carmichael et al. 2012), but the substrate of these changes remains undefined. An important future direction for EEG-fMRI in the study of seizures is the so-called pre-ictal state, which has been investigated with fMRI, preictal SPECT and also optical imaging. Some of the best data comes from intra-operative optical imaging which shows that focal alterations in cerebral haemodynamics precede seizure, sometimes by up to 20 seconds (Zhao, Suh et al. 2007). Further investigation into this effect has shown that changes in cerebral blood flow around the seizure focus occur up to minutes prior to seizure onset without concomitant alterations in cerebral metabolism, raising new questions regarding the underlying cause of these ‘early BOLD signal changes’ (Zhao, Nguyen et al. 2011) and revisiting the question of the validity of the assumption of ‘normal physiological’ neurovascular coupling in and around the seizure onset zone. Exciting new work from this group suggests that spatial correlation between haemodynamic and neuro-electric signals only occur for very brief periods during seizures and this knowledge may add to our interpretation of the changes observed in EEG-fMRI studies of ictal events (Ma, Zhao et al. 2013). The development of icEEG-fMRI allows a unique opportunity to investigate the neuronal substrate of these effects and the fact that I was able to record a single seizure using this technique is an important development. Further preliminary analysis of this activity using a frequency based model has yielded promising results and it seems likely, given the fact that LFPs relate so closely to BOLD signal, that analysis of high frequency activity will be an area of particular interest in the analysis of this type of data.
11.3.2 From Zones to Networks: using connectivity to inform interpretation of EEG-fMRI

Focal epilepsy is increasingly thought of as a disease of cerebral networks and more robust understanding of these networks is likely to result in improved ability to identify the best strategies for surgical intervention and possibly predict outcome (Aubert, Wendling et al. 2009, Negishi, Martuzzi et al. 2011) and see detailed discussion in section 2.14 both with regard to seizures and potential functional deficit. Given these developments, the work presented in this thesis, aimed to investigate methodology which could look beyond the seizure onset zone and give insight into how the epileptic network behaves in non-invasive data. In my study of FCD I was able to demonstrate that regions of BOLD signal change often lay outside the seizure onset zone, but within the irritative zone, suggesting they were involved in the epileptic network, although I did not study connectivity between the regions identified in that experiment. The use of simultaneous recording of electrical source imaging with EEG-fMRI has improved our interpretation of such regions, suggesting that it is possible to identify regions of BOLD signal change corresponding to initiation and propagation of interictal activity (Groening, Brodbeck et al. 2009, Vulliemoz, Thornton et al. 2009).

The results of the DCM analysis presented in chapter 8, suggest that DCM is a powerful tool for interrogating the effect of IEDs on the epileptic network, although the methods require further refinement and future directions include investigating the application of DCM to more complex neuronal models and studying interactions with cognitive networks in a more systematic way.
11.3.3 Translation to surgical planning: What is the role of EEG-fMRI?

In 2007, in the light of increasing data suggesting that EEG-fMRI might be an exciting new addition to the non-invasive identification of the epileptic focus, I aimed to investigate the role of the technique in pre-surgical evaluation.

Given the increasing body of evidence that sophisticated analysis of EEG-fMRI data can provide useful evaluation of the epileptic network there is a temptation to use this not only in informing surgical planning, but specifically integration in surgical systems. While I was able to demonstrate results which were concordant with IZ and EZ, it is important to emphasise that concordance is remains limited by the voxel size in fMRI, signal drop out (particularly in the temporal lobes) and intra-operative and post-operative brain shift (Nimsky, Ganslandt et al. 2000). Successful high field EEG-fMRI (Neuner, Warbrick et al. 2013) with minimal geometric distortion may lead to some improvement in resolution, but despite the technical ability to integrate this data into surgical guidance systems and the advent of intra-operative MRI (Schulz 2012) the routine reliable integration of fMRI data to guide surgery is some way off.

Although the various experiments have yielded some promising results, and unbiased sequential comparison with the gold standard (icEEG and post-operative outcome) was necessary, it is clear that the technique, in a clinical context, is only applicable to a small and highly selected group of patients – those who have focal epilepsy amenable to surgery (an estimated 3% of all patients developing epilepsy), who may require icEEG to localize the seizure (between 15 and 55% of those with refractory focal epilepsy depending on seizure syndrome (Noe K and et al. 2013)) and also have very frequent IEDs. This issue is shared with high resolution EEG, ictal SPECT, PET and MEG, all of which are most applicable to a similar group of patients in whom they add
various complementary pieces of information. Its role in pre-surgical evaluation, therefore, is likely to be as another addition to the battery of non-invasive tests which are currently used to evaluate this patient group, in the development of robust hypotheses for icEEG implantation. It should also be highlighted, that the results of these experiments demonstrate a relationship between widespread IED-related BOLD signal change and poor outcome, suggesting a potential role for excluding unsuitable candidates for icEEG. This is important as icEEG continues to be risky with relatively low rates of seizure freedom, both because resection is not always possible as well as the possibility of unsuccessful resection (McGonigal, Bartolomei et al. 2007, de Tisi, Bell et al. 2011, Holtkamp, Sharan et al. 2012, Noe K and et al. 2013).

Despite some of the limitations discussed above, the technique has promise, particularly in the light of evolving methods to improve both scanning techniques and analysis (as well as improved understanding of the neuronal substrates of the hemodynamic changes in epilepsy). It seems, that although it has a somewhat limited role in presurgical evaluation, EEG-fMRI, which offers the possibility of combining information from both neuronal and haemodynamic sources, remains one of the only true ‘multimodal’ techniques and with the evolving methodological and neurobiological developments discussed here is likely to continue to contribute to our understanding of the behaviour of the epileptic brain, both in relation to the epileptic network and its interaction with normal cerebral function.
12 APPENDIX A: CONSENT FORM

University College London Hospitals
NHS Foundation Trust
The National Hospital for Neurology and Neurosurgery
Epilepsy Department (box 20)
Queen Square, London, WC1N 3BG

CONSENT FORM

Principal Investigator: Professor Louis Lemieux; REC reference number: 04/Q0502/89

Patient Identification Number for this study:

Title of project: MR Imaging of Brain Generators in Human Epilepsy

1. I confirm that I have read and understood the information sheet dated February 2009 version 1.5 for the above study and have had the opportunity to ask questions.

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study.

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that sections of any of my medical notes (if any) may be looked at by responsible individuals from UCLH or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

5. I agree to take part in the above study.

6. I agree to a video recording of the experiment.

__________________________   ____________________________
Name of participant               Date                      Signature

__________________________   ____________________________
Name of Person taking consent    Date                      Signature
(if different from researcher)

If there are any problems, please contact Dr Rachel Thornton or Dr Umair Chaudhary (see information sheet for details)

Comments or concerns during the study
If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top this consent form.

__________________________   ____________________________
Name of Person taking consent    Date                      Signature
(if different from researcher)
13 BIBLIOGRAPHY


artifact-free electroencephalogram during functional magnetic resonance imaging.\textit{Neuroimage} 19(2 Pt 1): 281-295.


Benetti, S., A. Mechelli, M. Picchioni, M. Broome, S. Williams and P. McGuire (2009). "Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state." Brain 132(Pt 9): 2426-2436.


Binder, J. R. (2010). "Functional MRI is a valid noninvasive alternative to Wada testing." Epilepsy Behav.


surgery in patients with normal preoperative MRI. " J Neurol Neurosurg Psychiatry 76(5): 710-713.


Simultaneous In Vivo Optical Imaging of Neural Activity and Local Blood Volume." Cerebral Cortex 23(4): 885-899.


resonance imaging contrasts in MRI-negative refractory focal epilepsy." Epilepsia 48(2): 229-237.


parenchymal changes in complex partial status epilepticus. "**Brain** 128(Pt 6): 1369-1376.


