Hippocampal-Neocortical Networks underlying Episodic Memory and their Clinical Relevance in Medial Temporal Lobe Epilepsy

by

Cornelia McCormick

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Sciences
University of Toronto

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Doctor of Philosophy

Institute of Medical Sciences
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Abstract

The hippocampus is strongly structurally and functionally connected to one of the core resting state networks of the human brain, the Default Mode Network (DMN). In addition, regions of the DMN are often co-activated with the hippocampus during episodic autobiographical memory (AM) retrieval tasks. Patients with unilateral medial temporal lobe epilepsy (mTLE) are characterized by a reasonably focal damage to the hippocampus and a specific episodic memory deficit, therefore offering the opportunity to examine the impact of hippocampal damage on DMN connectivity and how these disruptions map onto the specific deficit in episodic memory capacity. Together, these findings led to the main focus of the current thesis; that is to examine how hippocampal-neocortical networks underlying episodic memory are affected by mTLE. The first two studies of this thesis focused on resting state DMN connectivity in patients with mTLE, and revealed that functional connectivity between both hippocampi and the posterior part of the DMN, including the posterior cingulate cortex (PCC) was indicative of episodic memory capacity in this patient population. The last two studies of this thesis focused on how the hippocampus is at the center of transient episodic AM networks. In healthy controls, we were able to show that the left hippocampus was connected to different sets of brain regions during different stages of AM retrieval, construction and elaboration. Lastly, this flexible hippocampal-
neocortical interplay was hindered in patients with mTLE. Together, we conclude that DMN connectivity reflects episodic memory capacity in patients with mTLE and might be of potential use in the clinical management in this patient population. Additionally, our data provide evidence that episodic memory is supported by an extensive repertoire of flexible, transient hippocampal-neocortical networks and that these dynamic networks extend beyond the regions of the DMN centering on the hippocampus as a major episodic memory hub of the brain.
Acknowledgments

First of all, I would like to thank my supervisor, Mary Pat McAndrews for the opportunity to come back to Toronto in 2009 to fulfill my dream of pursuing a career in memory research and to finally unite on one continent and in one city with my husband! In these last years, I learned a tremendous amount from you, Mary Pat, about the methodological approaches to brain connectivity and that it is possible to work 150% of the time (I think you normally break it down to 50% as a clinical neuropsychologist, 50% as a researcher and 50% as a supervisor). Amazingly, despite your work load I felt your commitment and guidance on this thesis project at all times!

I would further like to thank Morris Moscovitch for the inviting email I received back in 2005 in which you agreed to supervise a small research internship and made it possible for me to come to Toronto for six months. It turned out to be truly life changing, as I met my husband, Mary Pat and many of my current colleagues and friends back then. Thank you also for supporting me when I returned to pursue my PhD with Mary Pat, for letting me participate at your lab meetings and for sharing so many historic insights into memory research.

Thanks to both of you, you are such great and complementary inspirations for me in my path pursuing memory research! I remember reading the same paper for both lab meetings and being surprised of how little overlap in the topic of the discussion there was. At your lab meeting, Mary Pat, we scrutinized every bit of the methods section, and at your lab meeting, Morris, we pulled apart all the conceptual details and implications.

I would also like to thank the rest of my PhD committee, Adrian Crawley and Taufik Valiante, for their time and advice on this project. Thanks, Adrian for all the great questions and help with resting state connectivity analyses. Thanks, Taufik for your skill as a neurosurgeon and the great discussions about neuronal oscillations! Thanks also to Randy McIntosh for agreeing to join my Final PhD committee meeting and for reading all these pages!

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Contributions

I, Cornelia McCormick, solely prepared this thesis. I was involved in all aspects of this work, including the planning, execution, analysis, and writing of all original research and publications. The following contributions by other individuals are formally and inclusively acknowledged:

Dr. Mary Pat McAndrews (Primary Supervisor): Mentorship, laboratory resources, collection of resting state fMRI data, obtaining clinical information, including neuropsychological assessment of patients with mTLE, guidance and assistance in planning, execution, and analysis of experiments as well as manuscript and thesis preparation.

Dr. Morris Moscovitch (Thesis Committee Member): Mentorship, guidance and assistance in the interpretation of results as well as thesis preparation.

Dr. Taufik Valiante (Thesis Committee Member): Mentorship, clinical assessment of patients with mTLE, performance of all epilepsy surgeries, guidance and assistance in the interpretation of results, and preparation of manuscripts and the thesis.

Dr. Adrian Crawley (Thesis Committee Member): Mentorship, guidance and assistance in the interpretation of results as well as thesis preparation.

Dr. Randy McIntosh (Guest of the Final PhD Committee Meeting): Assistance in the thesis preparation.

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Irene Giannoylis: assistance in collection and analyses of fMRI data

Areeba Adnan: assistance in collection of fMRI data
## Table of Contents

Acknowledgments ........................................................................................................... iv

Contributions ...................................................................................................................... vi

List of Abbreviations ......................................................................................................... xii

List of Tables ....................................................................................................................... xiv

List of Figures ....................................................................................................................... xv

1 Literature Review ............................................................................................................. 1
   1.1 Overview ...................................................................................................................... 2
   1.2 Networks of the Brain ................................................................................................. 4
      1.2.1 Types of Brain Networks and Methods to Study them ........................................ 5
      1.2.2 General Findings of Network Analyses .................................................................. 9
      1.2.3 Summary .............................................................................................................. 19
   1.3 Networks of the Medial Temporal Lobe underlying Episodic Memory ............... 20
      1.3.1 The Medial Temporal Lobes and Episodic Memory .............................................. 20
      1.3.2 Hippocampal-Neocortical Network Interactions ................................................ 25
      1.3.3 Summary .............................................................................................................. 33
   1.4 Network Disruptions in Medial Temporal Lobe Epilepsy ......................................... 34
      1.4.1 Focusing on the MTL in mTLE ............................................................................ 34
      1.4.2 Network Disruptions in Medial Temporal Lobe Epilepsy ....................................... 44
      1.4.3 Summary .............................................................................................................. 52

2 Research Aims and Hypotheses ...................................................................................... 53
   2.1 DMN Connectivity and Episodic Memory Capacity in Patients with mTLE ............... 54
      2.1.1 Specific Hypotheses for the First Study ................................................................. 55
      2.1.2 Specific Hypotheses for the Second Study ............................................................ 55
   2.2 Flexible hippocampal-neocortical interactions during AM retrieval ..................... 56
      2.2.1 Specific Hypotheses for the Third Study ............................................................... 57
      2.2.2 Specific Hypotheses for the Fourth Study ............................................................ 57
3 Default Mode Network Connectivity indicates Episodic Memory Capacity in Medial Temporal Lobe Epilepsy ................................................................. 58

3.1 Abstract .......................................................................................... 59
3.2 Introduction ...................................................................................... 60
3.3 Methods .......................................................................................... 61
   3.3.1 Participants ............................................................................... 61
   3.3.2 MRI Acquisition and Preprocessing ......................................... 62
   3.3.3 Data Analysis .......................................................................... 64
   3.3.4 Episodic Memory Measures .................................................... 66
   3.3.5 Correlations between PCC-HC Connectivity and Episodic Memory Measures ................................................................. 67
   3.3.6 Comparison between Predictors .............................................. 67
3.4 Results ............................................................................................. 68
   3.4.1 DMN Disruptions in Patients with mTLE ....................................... 68
   3.4.2 Presurgical Status of PCC-HC Connectivity and Memory .......... 71
   3.4.3 Prediction of Postsurgical Memory Change ............................... 71
   3.4.4 Postsurgical Status of PCC-HC Connectivity and Memory ........ 76
   3.4.5 Comparison between Standard Predictors and PCC-HC Connectivity .................................................................................. 77
3.5 Discussion ......................................................................................... 78
3.6 Conclusions ...................................................................................... 80

4 Linking DMN Connectivity to Episodic Memory Capacity: What can we learn from Patients with Medial Temporal Lobe Damage ........................................ 81

4.1 Abstract ......................................................................................... 82
4.2 Introduction .................................................................................... 83
4.3 Materials and Methods ................................................................... 85
   4.3.1 Participants .............................................................................. 85
   4.3.2 Verbal and visuospatial memory components ........................... 85
   4.3.3 MRI acquisition ...................................................................... 87
   4.3.4 Regions of interest .................................................................. 87
   4.3.5 fMRI preprocessing and functional connectivity matrices of the DMN .................................................................................. 87
   4.3.6 Voxel-based morphometry and GMV of the DMN ..................... 88
   4.3.7 Statistical analyses .................................................................. 88
4.4 Results ............................................................................................ 90
   4.4.1 Structural damage and functional connectivity alterations of the DMN in mTLE ................................................................. 90
   4.4.2 Functional connectivity patterns related to individual differences in episodic memory capacity .................................................. 95
4.4.3 Relationship of combined structural damage and functional connectivity alterations to predicting episodic memory capacity

4.5 Discussion

4.6 Conclusions

5 Functional and Effective Hippocampal-Neocortical Connectivity during Construction and Elaboration of Autobiographical Memory Retrieval

5.1 Abstract

5.2 Introduction

5.3 Materials and Methods

5.3.1 Participants

5.3.2 Experimental Procedure

5.3.3 Data Acquisition

5.3.4 Data Analysis

5.4 Results

5.4.1 Behavioral Results

5.4.2 Early Hippocampal Activation

5.4.3 Functional Hippocampal-Neocortical Connectivity during AM Retrieval

5.4.4 Directed Hippocampal-Neocortical Connectivity during AM Retrieval

5.5 Discussion

5.5.1 AM Construction: Hippocampal-Fronto-Temporal Connectivity

5.5.2 AM Elaboration: Hippocampal-Temporo-Parieto-Occipital Connectivity

5.5.3 The Role of the Hippocampus in AM Retrieval

5.6 Limitations and Future Directions

5.7 Conclusions

6 Connectivity Changes during Construction and Elaboration of Autobiographical Memories in Patients with Medial Temporal Lobe Epilepsy

6.1 Introduction

6.2 Methods

6.2.1 Participants

6.2.2 Experimental Procedure

6.2.3 Data Acquisition

6.2.4 Data Analysis

6.3 Results

6.3.1 Univariate contrasts

6.3.2 Dynamical Functional Hippocampal-Neocortical Connectivity
6.4 Discussion .................................................................................................................. 145
6.5 Conclusions ........................................................................................................... 148

7 General Discussion ................................................................................................... 149
7.1 Summary of Findings .............................................................................................. 150
7.2 Hippocampal-Neocortical Network Disruptions in Patients with mTLE .... 152
  7.2.1 Structural Integrity of the Epileptogenic MTL and its Relationship
to Episodic Memory Capacity .............................................................................. 152
  7.2.2 Functional Integrity of the Epileptogenic MTL and its Relationship
to Episodic Memory Capacity .............................................................................. 154
  7.2.3 Decreased DMN Connectivity in Patients with mTLE ............................ 155
  7.2.4 Increased DMN Connectivity in Patients with mTLE .............................. 156
  7.2.5 Flexible Network Changes in Patients with mTLE: Neuronal Context ............................................................ 158
  7.2.6 Alternative Networks supporting AM Retrieval in Patients with mTLE .... 158
  7.2.7 Clinical Relevance of Network Integrity in Patients with mTLE ......... 159

7.3 Hippocampal-Neocortical Networks underlying Episodic Memory .......... 160
  7.3.1 Fractionation of Hippocampal Contribution to Autobiographical Memory ................................................................. 160
  7.3.2 Hippocampus as a Critical Hub for Episodic Memory .......................... 161
  7.3.3 The Default Mode Network and Episodic Memory ............................... 162

7.4 Networks of the Brain ............................................................................................ 164
  7.4.1 Functional Network Consequences of Local Structural Damage ....... 164
  7.4.2 Functional Neuronal Networks enabling Cognition ............................... 166

8 Limitations and Future Directions ........................................................................... 168
8.1 Predicting Memory Outcome at an Individual Level ......................................... 169
8.2 Predictive Power of Resting State fMRI in Comparison to Task-Based fMRI .......................................................................................................................... 170
8.3 Autobiographical Memory Retrieval in Patients with mTLE ........................ 171
8.4 Spatiotemporal Functional Connectivity in Patients with mTLE ................ 172
8.5 Computational Simulation of MTL Damage ....................................................... 173
8.6 Neuronal Context of the Hippocampus .............................................................. 174

9 Conclusions .............................................................................................................. 176

References .................................................................................................................... 178

Copyright Acknowledgements ..................................................................................... 205
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALE</td>
<td>Activation Likelihood Estimation</td>
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<tr>
<td>AM</td>
<td>Autobiographical Memory</td>
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<tr>
<td>amPFC</td>
<td>Anterior Medial PFC</td>
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<td>BIC</td>
<td>Binding in Context</td>
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<td>BOLD</td>
<td>Blood-Oxygen-Level-Dependent</td>
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<tr>
<td>BSR</td>
<td>Bootstrap Ratio</td>
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<tr>
<td>DCM</td>
<td>Dynamic Causal Modeling</td>
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<tr>
<td>dlPFC</td>
<td>Dorsolateral PFC</td>
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<tr>
<td>DMN</td>
<td>Default Mode Network</td>
</tr>
<tr>
<td>dmPFC</td>
<td>Dorsomedial PFC</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EPI</td>
<td>Echo Planar Imaging</td>
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<td>fMRI</td>
<td>Functional MRI</td>
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<tr>
<td>FWHM</td>
<td>Full Width Half Maximum</td>
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<td>GMV</td>
<td>Grey Matter Volume</td>
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<tr>
<td>HC</td>
<td>Hippocampus</td>
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<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
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<tr>
<td>iEEG</td>
<td>Intracranial EEG</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>IPL</td>
<td>Inferior Parietal Lobule</td>
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<tr>
<td>LTC</td>
<td>Lateral Temporal Cortex</td>
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<tr>
<td>LV</td>
<td>Latent Variable</td>
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<tr>
<td>MACM</td>
<td>Meta-Analytic Connectivity Modeling</td>
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<tr>
<td>MEG</td>
<td>Magnetoencephalography</td>
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<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MTL</td>
<td>Medial Temporal Lobe</td>
</tr>
<tr>
<td>mTLE</td>
<td>Medial Temporal Lobe Epilepsy</td>
</tr>
<tr>
<td>MTS</td>
<td>Medial Temporal Lobe Sclerosis</td>
</tr>
<tr>
<td>OBI</td>
<td>Ontario Brain Institute</td>
</tr>
<tr>
<td>PCC</td>
<td>Posterior Cingulate Cortex</td>
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<tr>
<td>PCC-HC</td>
<td>Functional Connectivity between PCC and Hippocampus</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PFC</td>
<td>Prefrontal Cortex</td>
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<td>PHC</td>
<td>Parahippocampal Cortex</td>
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<tr>
<td>PLS</td>
<td>Partial Least Squares</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
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<tr>
<td>RSP cortex</td>
<td>Retrosplenial Cortex</td>
</tr>
<tr>
<td>SCN</td>
<td>Structural Covariance Networks</td>
</tr>
<tr>
<td>SEM</td>
<td>Structural Equation Modeling</td>
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<tr>
<td>SVD</td>
<td>Singular Value Decomposition</td>
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<tr>
<td>TempP</td>
<td>Temporal Pole</td>
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<tr>
<td>TPJ</td>
<td>Temporoparietal Junction</td>
</tr>
<tr>
<td>UHN</td>
<td>University Health Network</td>
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<tr>
<td>VBM</td>
<td>Voxel Based Morphometry</td>
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<tr>
<td>vlPFC</td>
<td>Ventrolateral PFC</td>
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<tr>
<td>vmPFC</td>
<td>Ventromedial PFC</td>
</tr>
<tr>
<td>WFR</td>
<td>Warrington's Faces Recognition Test</td>
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<tr>
<td>WWR</td>
<td>Warrington's Words Recognition Test</td>
</tr>
</tbody>
</table>
List of Tables

Table 3.1: Demographical and Clinical Information (Study 1) .......................................................... 63

Table 3.2: DMN Regions of Interest and MNI Coordinates ............................................................. 65

Table 3.3: Comparison between Standard Predictors and PCC-HC Connectivity ...................... 77

Table 4.1: Demographical and Clinical Information (Study 2) ......................................................... 86

Table 4.2: Grey Matter Volume Differences within the DMN between Healthy Controls and Patients with mTLE .................................................................................................................. 93

Table 4.3: Functional Connectivity Differences within the DMN between Healthy Controls and Patients with mTLE .................................................................................................................. 93

Table 4.4: Functional Connectivity within the DMN indicates Episodic Memory Capacity in Patients with mTLE .................................................................................................................. 98

Table 5.1: Hippocampal Peak Coordinates during AM Retrieval in Healthy Controls ............ 117

Table 5.2: Whole Brain Peak Coordinates during AM Retrieval in Healthy Controls .......... 118

Table 5.3: Functional Hippocampal-Neocortical Connectivity during AM Retrieval ............ 122

Table 6.1: Demographical and Clinical Information (Study 4) ......................................................... 136

Table 6.2: Peak Coordinates of Activated Brain Regions during AM Retrieval in Healthy Controls .................................................................................................................................................. 139

Table 6.3: Peak Coordinates of Activated Brain Regions during AM Retrieval in Patients with Left mTLE .................................................................................................................................................. 140

Table 6.4: Peak Coordinates of Differences in Brain Activation during AM Retrieval in Healthy Controls and Patients with Left mTLE .................................................................................................................................................. 142
List of Figures

Figure 1.1: Early Summary of Deactivations within DMN Regions ........................................ 14
Figure 1.2: Hippocampal-Neocortical Connectivity and Relation to the DMN ..................... 27
Figure 1.3: DMN Disruptions in Patients with mTLE .......................................................... 48
Figure 1.4: AM Retrieval and Functional Network Disruptions in Patients with mTLE ....... 51
Figure 3.1: Hippocampal Degree as a Function of Threshold ............................................. 66
Figure 3.2: DMN Connectivity in Healthy Controls and Patients with mTLE ..................... 69
Figure 3.3: Degree Distribution for all DMN Regions ......................................................... 70
Figure 3.4: Hierarchical Clustering of DMN Connectivity ................................................. 70
Figure 3.5: PCC-to-Voxel Connectivity in Healthy Controls and Patients with mTLE ......... 72
Figure 3.6: Presurgical Status of PCC-HC Connectivity and Episodic Memory Capacity ...... 73
Figure 3.7: Prediction of Postsurgical Episodic Memory Change ....................................... 74
Figure 3.8: Postsurgical Status of PCC-HC Connectivity and Episodic Memory ............... 75
Figure 3.9: Spread of Functional Connectivity Values ..................................................... 76
Figure 4.1: Functional Connectivity within the DMN in Healthy Controls and Patients with mTLE .................................................................................................................. 92
Figure 4.2: Structural and Functional DMN Integrity Differences between Healthy Controls and Patients with mTLE ........................................................................................................ 96
Figure 4.3: Functional Connectivity Alterations of the DMN and Episodic Memory Capacity in Patients with mTLE ........................................................................................................ 97
Figure 4.4: PCC-HC Connectivity indicates Episodic Memory Capacity in Patients with mTLE ............................................................................................................................. 100

Figure 4.5: Comparison between DMN and PCC-HC to indicate Episodic Memory Capacity in Patients with mTLE ............................................................................................................................. 101

Figure 5.1: Temporal Characteristics of Hippocampal Activation during AM Retrieval .......... 117

Figure 5.2: Functional Hippocampal-Neocortical Networks during AM Retrieval ............... 121

Figure 5.3: Mean-Based Contrast between Construction and Elaboration of AM Retrieval ..... 122

Figure 5.4: Location of SEM Nodes and Relation to the Seed ................................................. 124

Figure 5.5: Effective Hippocampal-Neocortical Networks during AM Retrieval in Healthy Controls................................................................................................................................. 125

Figure 6.1: Activated Brain Regions during AM Retrieval in Healthy Controls ................. 138

Figure 6.2: Activated Brain Regions during AM Retrieval in Patients with Left mTLE ......... 140

Figure 6.3: Difference in Brain Activation during AM Retrieval in Healthy Controls and Patients with Left mTLE ................................................................................................................................. 141

Figure 6.4: Hippocampal-Neocortical Networks during AM Retrieval in Healthy Controls and Patients with Left mTLE ................................................................................................................................. 143

Figure 6.5: Functional Connectivity between anterior left and right hippocampus in controls and patients with L-mTLE ................................................................................................................................. 144
1 Literature Review
1.1 Overview

The human brain contains approximately 85 billion neurons that are intricately connected, forming a network that is uniquely suited to guide behavior and shape cognition (Azevedo, Carvalho et al. 2009). This anatomical web forms the foundation upon which an extensive functional repertoire supports various kinds of human cognition, such as our ability to mentally travel back or forward in time and experience vivid, detail-rich mental imagery. With the development of magnetic resonance imaging (MRI), we now have the capability to explore this tremendous network in vivo. These new technologies and application of novel analytic techniques are evolving rapidly to enhance our understanding of how this biological neural network supports cognition.

Network studies of the brain are beginning to unravel one core network, concentrating around the posterior cingulate cortex (PCC), medial prefrontal cortex, lateral parietal cortices and medial temporal lobes (Hagmann, Cammoun et al. 2008; van den Heuvel and Sporns 2011). This core network, sometimes called the Default Mode Network (DMN), is characterized by strong anatomical connections and it is highly functionally connected even during wakeful rest (Shulman, Fiez et al. 1997; Raichle, MacLeod et al. 2001; Buckner, Andrews-Hanna et al. 2008; Honey, Sporns et al. 2009).

However, this core network is everything but a static phenomenon, even at rest. Arguably, functional connectivity measured over a long period of time reflects the anatomical brain structure accurately. However, at shorter time scales, numerous functional networks are formed and dissolved, and formed again into different constellations, exploring possible configurations of functional subnetworks (Honey, Kotter et al. 2007; Deco, Jirsa et al. 2011). Then, responding to a specific task, the idea is that some of these connections become engaged, forming transient process-specific alliances to successfully complete the task at hand (Moscovitch 1992; McIntosh 1999; McIntosh 2000; Cabeza and Moscovitch 2013). These process-specific alliances are not random but reflect the functional specialization of each brain region.
This dynamic network portrayal can be illustrated by exploring the hippocampus and adjacent medial temporal lobe (MTL) structures which are part of this core network and play a critical role in episodic memory retrieval, our ability to remember past events that are specific in place and in time (Tulving 1983; Tulving 2002). Patient data have demonstrated that bilateral damage to the MTL, including the hippocampi leads to severe anterograde and retrograde amnesia for autobiographical events, indicating the absolute criticality of this brain region to episodic memory function (Milner and Penfield 1955; Scoville and Milner 1957; Steinworth, Levine et al. 2005). However, neuroimaging studies have illustrated that during episodic memory retrieval tasks not only the MTL but also a set of other brain regions, mainly the constituents of the DMN, become activated (Maguire 2001; Svoboda, McKinnon et al. 2006; Rugg and Vilberg 2013).

From this perspective, the regions of the DMN can be seen as common alliances of the MTL in supporting this multifaceted cognitive task. At a closer look, each particular instance of episodic remembering however requires its additional process-specific alliance between the MTL and other brain regions beyond the DMN. For example, the hippocampus, thought to bind items into their context (Eichenbaum, Yonelinas et al. 2007; Ranganath 2010), and part of the fusiform cortex, considered the key region in face perception and identification (Kanwisher, McDermott et al. 1997), bond transiently during relational face processing (McCormick, Moscovitch et al. 2010). Thus, the MTL appears to be bound into a general network substantially overlapping with the DMN that supports episodic memory function across tasks but also to have the ability to form transient connections to highly specialized partners that support the unique task demand at hand. Thus, the MTL might be characterized as the main hub within the episodic memory domain.

Patients with medial temporal lobe epilepsy (mTLE) offer the opportunity to study the effects of unilateral MTL damage on this dynamic network arrangement. For example, DMN connectivity, especially between the PCC and the affected MTL has been shown to be reduced in this patient population (Waites, Briellmann et al. 2006; Voets, Beckmann et al. 2012), suggesting that even the basic communication between the MTL and its partners is dysfunctional. Further, some lines of evidence suggest that mTLE decreases the capability of the hippocampus to explore possible functional subnetworks, therefore not being able to form transient connections among specialized brain regions (Protzner, Valiante et al. 2010; Protzner, Kovacevic et al. 2013). Although there are no studies that directly examine this flexible online recruitment of subnetworks, it is interesting to note that patients with mTLE have been reported to recruit different networks than
healthy controls during some episodic memory tasks, in that they do not rely on hippocampal connectivity (Addis, Moscovitch et al. 2007).

The main goal of the current thesis is to examine hippocampal-neocortical networks underlying episodic memory and how mTLE affects this interplay during rest and during AM retrieval. The first two studies concentrate on how hippocampal-DMN disruptions map onto the clinical episodic memory deficit seen in patients with mTLE. As will become apparent, the connections between the damaged MTL and the posterior parts of the DMN appear to be especially indicative of episodic memory function and have the potential to be used in the clinical setting to assess this cognitive capacity. The last two studies focus on how the hippocampus is at the centre of transient connections that differ between two stages of autobiographical memory (AM) retrieval and how this flexibility is affected by mTLE. Here, we show that healthy hippocampi can form transient networks including a wide range of brain regions, also beyond its general DMN partners. In patients with mTLE, this flexibility is hindered, leading to major alterations in the networks underlying episodic AM retrieval. Together, this thesis show that hippocampal-neocortical networks are disrupted in patients with mTLE and that especially the interhemispheric connectivity between both hippocampi and posterior brain regions, including visual-perceptual areas may be important to support vivid, detail-rich episodic memory function.

In order to introduce the background to the current research questions, the following literature review will focus on three main research themes: networks of the brain, hippocampal-neocortical networks underlying episodic memory, and hippocampal-neocortical network disruptions in patients with mTLE.

### 1.2 Networks of the Brain

The formation of single elements into large, interconnected complex networks can be found virtually everywhere in nature, from colonies of bacteria, to shoals of fish, to flocks of birds, and human social structures. Here, formal network analyses approaches can provide fundamental insights into how these single elements interact with each other to form dynamic patterns. The
brain is no exception; the collective interactions of millions of neurons guide behavior, shape thought, and form and retrieve memories. Understanding these integrative dynamics and their relation to behavior requires methodological approaches suitable for network analyses.

1.2.1 Types of Brain Networks and Methods to Study them

Brain networks span multiple scales, from the microscale of individual cells and synapses to the macroscale of cognitive systems. These levels do not exist in isolation; rather patterns at each level critically depend on processes unfolding on both lower and higher levels. Therefore, brain function can only be fully understood by identifying brain networks at all levels. That is, binding cells into a coherent population, organizing cell groups into functional brain regions, integrating regions into systems, and linking brain and body into a complete behaving organism. This hierarchy and the resulting explorations of multiscale network interactions will be crucial to relate molecules and cells to behavior and cognition. This major endeavor describes the main thesis of the Human Brain Connectome Project (http://www.humanconnectomeproject.org) in a nutshell (Sporns, Tononi et al. 2005; Sporns 2013). The current PhD thesis focuses mainly on one level, namely the interactions between brain regions that support a specific cognitive domain, however, reference to other levels will be made where applicable.

Given the current interest in brain connectivity, it is not surprising that there are several important measures to refine network analyses in humans. Brain connectivity can be derived from histological sections, derived from postmortem brains or surgical resections that reveal anatomical connections, from single-cell recordings of a small number of neurons, and from functional imaging of the entire brain. Perhaps the most important distinction of brain connectivity is between structural connectivity as a “wiring diagram” of physical anatomical links and functional connectivity as a web of “dynamic interactions” which do not necessarily follow physical links one-to-one.

1.2.1.1 Structural Connectivity

Structural connectivity refers to a set of physical, anatomical connections linking neuronal elements. These anatomical connections range in scale from those of local circuits among single cells to large-scale networks of interregional pathways. Research ethics and human rights prohibit invasive tracer methods in humans, therefore limiting the exploration of structural
connectivity mostly to non-invasive but indirect alternatives. Therefore, a common way to measure these interregional pathways is the non-invasive method, diffusion tensor imaging (DTI, (Le Bihan, Mangin et al. 2001; Assaf and Pasternak 2008). DTI is a magnetic resonance imaging (MRI) technique that enables the measurement of restricted water molecules in tissue in order to produce maps of neuronal tract images. Another structural MRI method examines structural covariance networks (SCN) which are based on correlative approaches across participants (Bullmore, Woodruff et al. 1998; Lerch, Worsley et al. 2006; Evans 2013). Here, structural MRI is used to create an anatomical brain image and sophisticated analysis techniques, such as voxel based morphometry (VBM) are employed to derive estimates of grey matter volume (GMV) or cortical thickness (Eggert, Sommer et al. 2012). Correlating estimates from one brain region with all other regions across a number of participants provides then information about which brain regions co-vary in size or thickness. The neurobiological mechanisms that drive these cross-correlations are only partially understood and probably involve developmental and plasticity processes (Evans 2013). For example, examinations of SCNs revealed that large scale brain networks mature together (Raznahan, Lerch et al. 2011) and change due to experience (Bermudez, Lerch et al. 2009). Further, this approach was recently employed to analyze anatomical characteristics of large-scale brain networks (He, Chen et al. 2007) and continue to be developed in the clinical context (Bernhardt, Worsley et al. 2008; Bernhardt, Chen et al. 2011; Bernhardt, Hong et al. 2013).

1.2.1.2 Functional Connectivity

Functional connectivity refers to patterns of temporal correlations between distributed and often remote neurophysiological events (Friston 1994; Friston 2011). The basis of most types of functional connectivity stems from time series data from neuronal recordings, such as electroencephalography (EEG), intracranial EEG (iEEG), magnetoencephalography (MEG), and functional MRI (fMRI). Pairwise correlations of brain signals extracted from regions of interest (ROIs) provide a snapshot of functional connectivity patterns. This is perhaps the simplest and most often used method of examining functional connectivity. Bivariate statistical dependencies can be computed as cross-correlation or in the spectral domain as coherence and phase synchronization (Penny, Kiebel et al. 2002). The advantages of functional connectivity lies in its ability to allow mapping of statistical patterns of dynamic coupling between distributed brain regions which are not necessarily linked monosynaptically. Thus, functional connectivity can be
used to examine how distributed brain regions form a coherent network supporting a specific cognitive task. Whereas traditional approaches to functional imaging contrast two conditions with each other and compare the mean difference, correlational connectivity approaches can be used to examine how the relationship of two brain areas change due to different experimental conditions or in the context of different types of neural pathology. In that sense, functional connectivity allows examining the interaction effect between two brain regions and two experimental conditions or groups (McIntosh and Gonzalez-Lima 1994; McIntosh and B. 2013). However, as McIntosh et al. (2013) point out, calculating pairwise correlations becomes problematic when the number of correlations grows and correction for inflated false positive rates due to multiple statistical tests becomes necessary. At this point multivariate methods, such as independent component analysis (ICA) or seed partial least squares (PLS) become helpful (McIntosh, Bookstein et al. 1996; Krishnan, Williams et al. 2011). In short, ICA seeks out a set of independent components amongst a set of “signal mixtures” on the assumption that these independent components are derived from unrelated physical processes (Stone 2002). Applied to fMRI data for example, ICA yields a set of brain regions whose activity fluctuations vary together over time. If the time course of an independent component corresponds to the experimental design, the spatial layout of that component can then be seen as a functionally connected network. Another multivariate approach, seed PLS examines the relationship between a seed region and all other voxels in the context of changing experimental conditions or of different groups. At the heart of PLS lies the singular value decomposition (SVD) that allows the detection of functional connectivity patterns in one statistical step, rather than the massive amount of statistical tests used in typical univariate data analysis.

1.2.1.3 Effective Connectivity

Inherent to functional connectivity measures is that they rely on bidirectional correlations (e.g., A\(\rightarrow\)B), thus they cannot reveal how this connection is mediated, for example through unidirectional influences (e.g., A\(\rightarrow\)B) or via indirect interactions or due to a common external influence (e.g., C\(\rightarrow\)A and C\(\rightarrow\)B). Effective connectivity is therefore a logical progression from functional connectivity in that it attempts to examine causal effects between neurophysiological events (Friston 1994; Friston 2011) which can be inferred through time series analysis, statistical modeling, or experimental perturbations. Most effective connectivity estimation techniques, such as structural equation modeling (SEM (McIntosh and Gonzalez-Lima 1994; McIntosh and
Protzner 2012)) or dynamic causal modeling (DCM (Friston, Harrison et al. 2003; Kiebel, David et al. 2006; Stephan, Penny et al. 2010)), require the specification of an explicit causal model including structural parameters in which directional influences are then estimated. SEM is one of the earliest covariance based effective connectivity analysis applied to functional neuroimaging (McIntosh and Gonzalez-Lima 1994). The causal model of SEM is pre-determined by the experimenter who constructs a plausible anatomical model from known primate neuroanatomy. Mathematical limitations constrain the number of connections to be lower than the number of possible correlation coefficients among all included nodes. Through a number of iterations, SEM then allows the assignment of effective connectivity strengths (i.e., path coefficients) that best match observed covariance patterns recorded either from two different experimental conditions or groups. For example, an early use of SEM to fMRI data revealed altered patterns of effective connectivity among a distributed brain network underlying AM due to localized structural damage to the MTLs (Maguire, Vargha-Khadem et al. 2001).

1.2.1.4 Graph Theory approach to Networks

While the separation of structural and functional connectivity provide a rough operational framework to analyze brain connectivity, it is important to keep their interdependence and limitations in mind. In fact, one of the most important questions in the area of brain connectivity concerns the way in which structural and functional networks shape and constrain each other. The attempt to compare and combine measures of structural and functional connectivity accelerated the emergence of graph analysis into brain research (Bullmore and Sporns 2009; Bullmore and Bassett 2011). Graph analysis refers to a mathematical branch that deals with the formal description and analysis of graphs which are defined simply as a set of nodes linked by connections or edges which may be undirected (functional) or directed (effective). Graphs describe relative positions of network elements, rather than their accurate geometrical position, therefore providing an abstract representation of the system’s elements and interactions. The power of graph-based approaches stems from the fact that virtually all complex systems, including structural and functional brain data, can be meaningfully described as networks. The construction of brain graphs from empirical data contains several steps that include the selection of nodes and usually the thresholding of measures that determine whether two nodes are connected or not. Then, network parameters of interest can be calculated and compared to the equivalent parameter of a different population of brain data or random networks. As discussed in
greater detail in section 1.2.2, graph analysis has provided evidence that structural and functional brain networks display the same global topographical organization.

1.2.1.5 Computational Simulations of Networks

Another approach to study the interrelationship between structural and functional integrity is computational simulation (Honey and Sporns 2008; Honey, Sporns et al. 2009). Various high profile projects, such as the Virtual Brain in Canada (http://www.thevirtualbrain.org), the Blue Brain Project (http://bluebrain.epfl.ch/) in Switzerland and the Human Brain Project in Europe (https://www.humanbrainproject.eu) work on simulating brain activity taking into account various levels of structural and functional properties. The advantage of theoretical approaches is that they can re-create functional connectivity patterns based on local structural properties and pre-defined dynamics, thus helping to identify which properties might be essential to network function (Deco, Jirsa et al. 2011; Nakagawa, Jirsa et al. 2013). The theoretical network model of a healthy brain then opens the door to examine the consequences of structural impact, such as stroke to normal brain function which then allows generating informed hypothesis for empirical research (Honey and Sporns 2008; Alstott, Breakspear et al. 2009). An example of this instructive exchange between theoretical and empirical experiments will become apparent in section 0, in that virtual lesions predicted a specific pattern of functional connectivity changes which could be replicated empirically in a patient population with focal structural lesions.

1.2.2 General Findings of Network Analyses

Although still in its infancy, the field of brain connectivity is beginning to illuminate how different brain regions might work together to accomplish complex cognitive tasks. It appears that brain networks generally possess a hierarchical small world topology in which local regions are densely interconnected and a few key regions are characterized by a high number of connections to the rest of the network (Watts and Strogatz 1998). This small world topology suggests that individual brain regions are highly specialized and some “hub” structures might integrate processes across cognitive domains (Friston 1994; Bullmore and Sporns 2009).

1.2.2.1 Structural Core

The description of the human brain as a structural network can be encountered at all scales of brain research. These networks are perhaps most conveniently derived from the cellular level in
which small neuronal cell assemblies are connected by synapses. Structural network descriptions of the human brain date back to Cajal (Cajal 1906; Cajal 1995) and speculations about their functional relevance to Hebb (Hebb 1949). While there is extensive knowledge about structural connectivity map of other species, such as the macaque monkey (Stephan, Kamper et al. 2001; Stephan 2013), the lack of non-invasive methodology to examine structural connectivity in humans has the consequence that, up to today, “… the shameful [truth] is that we do not have such a detailed map” (Crick and Jones 1993). Nonetheless, DTI has made tremendous advances and as a result, more and more becomes known about the topology of structural human brain networks at a large scale. That is, brain networks are organized into small-world architecture, in which neighbouring nodes show more connections than nodes that are further apart (Watts and Strogatz 1998; Strogatz 2001). Within this small world organization, certain regions display a comparatively higher number of connections to the rest of the network, thus have been identified as hubs. A seminal DTI study in 2008 showed that large-scale brain networks form a structural core (Hagmann, Cammoun et al. 2008). In this study, the brain was partitioned into 66 anatomical subregions and the likelihood of an existent white matter connection between all regions was calculated. Then graph analytic measures that described how many connections a given subregion possesses (degree) and how many of the shortest paths between all other node pairs in the network would pass through it (centrality) were calculated. These analyzes revealed that some brain regions, including medial and lateral parietal cortices, were characterized by high degree and centrality, thus forming central hubs. Interestingly, this structural core overlaps significantly with the so called default mode network (DMN) which will be described in much more detail in section 1.2.2.3. To preview, the DMN consists of a number of structurally and functionally highly connected brain regions, together forming a collections of hubs (Buckner, Andrews-Hanna et al. 2008; Deco, Jirsa et al. 2011). In computational models, the importance of an individual node to network function can be assessed by virtually lesioning it, thus removing its effect on connectivity. Studies using this approach recently underscored the importance of the regions involved in the DMN by showing drastically decreased network function when lesioning a DMN node in comparison to a non-DMN node (Honey and Sporns 2008; Alstott, Breakspear et al. 2009).

Furthermore, a specific set of nodes, highly overlapping with the structural core and DMN, were found to be more densely interconnected than would be expected solely by their degree, together
forming a so-called rich club (van den Heuvel and Sporns 2011). That is, a large fraction of all shortest paths linking pairs of brain regions pass through the rich club and damage to rich club members has a more devastating effect of global network function than damage to a non-rich club member. Interestingly, these rich-club regions have long known roles in central human behavior, such as the hippocampus for episodic memory function, and it has been suggested that the rich club as a group integrates information from multiple cognitive domains (Whalley 2012; van den Heuvel and Sporns 2013; Misić, Sporns et al. 2014). Together, the emerging evidence from structural network analysis points to a central core of highly connected and mutually interconnected brain regions whose integrity, as will be described in the next section, plays a central role for global information flow and dynamical network function.

1.2.2.2 Neurocognitive Networks

At the functional systems level, most findings relating to neurocognitive networks stem from fMRI studies as this technique allows observing the entire brain at a reasonably high spatial and temporal resolution. At a 3 Tesla MRI scanner, commonly acquired voxel sizes of functional images are around 4 x 4 x 4 mm which opens the possibility to examine brain activity of different regions even in close proximity. The voxel size of high-resolution fMRI can be reduced to around 1 x 1 x 1 mm which permits separating the contributions of very specific brain subregions (Polimeni, Fischl et al. 2010). Unfortunately, high resolution fMRI as of now does not allow the coverage of the entire brain. The temporal resolution of fMRI is markedly slower than that of other neuroimaging tools, such as EEG and MEG, however, acquiring an image of the living brain every 2 seconds or so is still remarkable and allows one to observe changes in brain activation as a function of engagement in different cognitive processes.

A traditional, task-based fMRI protocol involves the acquisition of blood-oxygen-level-dependent (BOLD) time series while the participants in the scanner perform a pre-specified cognitive task, such as retrieving AMs. Activated brain regions can then be identified from contrasting BOLD signal during the task of interest to an interleaved control task. This approach expanded tremendously the knowledge about specialized brain regions and their contributions to cognitive processes. In fact, these carefully crafted experimental designs and observations of how experimental perturbations relate to changes in brain activity were essential in the discovery of the major functional brain networks known today. Interestingly, for some of these networks,
the brain regions that interact together to support a specific cognitive task also interact with each other during resting periods; that can be observed with resting state fMRI. During resting-state fMRI the participant is awake and no pre-specified task is performed (Biswal, Yetkin et al. 1995; Fox and Raichle 2007; Raichle 2011). Resting-state functional connectivity can then be derived from statistical dependencies, usually cross-correlations between voxels or ROIs. Despite the relatively unconstrained task description of “rest”, functional connectivity patterns of several networks have been shown to be remarkably consistent within and across individual participants (Damoiseaux, Rombouts et al. 2006; Van Dijk, Hedden et al. 2010) and to overlap substantially with co-activation patterns observed under task demand (Smith, Fox et al. 2009). As of now, these resting state networks have become a central tenet in the description of brain organization in healthy individuals and patients with various neurological diseases (Zhang and Raichle 2010; Castellanos, Di Martino et al. 2013; Kollndorfer, Fischmeister et al. 2013).

In fact, network analysis of whole brain fMRI data are beginning to converge on a consistent set of large-scale networks that comprise the building blocks of spontaneous and task-evoked brain dynamics (Meehan and Bressler 2012). These large-scale networks encompass a set of distinct anatomical regions that contributes to the integrity of a given behavioral domain and are now commonly referred to as “neurocognitive networks”. Whereas there is no final agreement on the exact definition of this term, one prominent account accredits them five cardinal properties (Mesulam 1990; Mesulam 2008; Mesulam 2012): First, network nodes can be localized cortically or subcortically and can function as critical or ancillary nodes. Whereas both types of nodes are activated during functional imaging, only damage to the critical node causes catastrophic impairment of the relevant behavior. Second, critical nodes are connected monosynaptically and become co-activated to support the relevant behavior. Third, each node, critical and ancillary, contributes a specialized component to the relevant behavior. Therefore, all nodes work collaboratively but not interchangeable. Fourth, the behavior emerges as a property of the entire network. Fifth, nodes can assemble into different networks, thus contributing their specialized function to support different behavioral outputs. Despite the numerous ways to apply connectivity and graph analytic approaches to resting state fMRI, the overall findings are surprisingly consistent in that there are a few major neurocognitive networks in the human brain. According to the definition of above, five major systems are considered neurocognitive networks: the fronto-parietal spatial network, the left hemisphere temporoperisylvian language
network, the limbic/paralimbic network for explicit memory and motivational salience, the inferotemporal face and object recognition network, and the prefrontal executive function (Mesulam 2008). Other classifications, based on resting state fMRI ICA analysis, distinguish the DMN, fronto-parietal attention network, the executive control network, the salience network, and sensorimotor, visual and auditory system (Doucet, Naveau et al. 2011; Raichle 2011). Interestingly, all of these central neurocognitive networks contained at least one rich club member, suggesting that integration of information between segregated functional domains evolve around one basic architectonic fundament (van den Heuvel and Sporns 2013). Together, these studies indicate that resting state fMRI can provide important insights into brain organization. As will become apparent in this thesis, resting state fMRI also has the capability to indicate the cognitive capacity that is performed by a specific neurocognitive network.

1.2.2.3 The Default Mode Network

The discovery of the DMN was accidental. Initially, the DMN was described but paid little attention to in early studies in which resting periods were included in task-based fMRI protocols to serve as a baseline against which relative activation and deactivation could be measured (Buckner, Petersen et al. 1995). However, in 1997 a seminal meta-analysis of these studies (see Figure 1.1) then revealed that activation in specific brain regions increased during resting periods as compared to the experimental, mostly goal-directed tasks (Shulman, Fiez et al. 1997). This meta-analysis illustrated explicitly the full extent of the DMN for the first time. Once made public, other influential research propelled the DMN into its own research field by giving it its own name, linking it to specific anatomical regions, and revealing that the DMN is distinguishable from other task-induced deactivations, such as attenuation of activity in unattended sensory regions (Gusnard, Akbudak et al. 2001; Raichle, MacLeod et al. 2001).

1.2.2.3.1 Structural and Functional Connectivity of the DMN

At first, the anatomy of the DMN was described using contrasts between resting and task states using positron emission tomography (PET (Shulman, Fiez et al. 1997; Raichle, MacLeod et al. 2001)). More recently, functional connectivity of resting state fMRI revealed a similar anatomical estimate of the DMN (Greicius, Krasnow et al. 2003; Fox and Raichle 2007). Its core regions comprise the anterior medial prefrontal cortex (amPFC), dorsomedial prefrontal cortex (dmPFC), posterior cingulate cortex (PCC), retrosplenial cortex (RSP), inferior parietal lobule
(IPL), lateral temporal cortex (LTC), and medial temporal lobe (MTL), including hippocampus, parahippocampal (PHC) and entorhinal cortex (Buckner, Andrews-Hanna et al. 2008). Remarkably, most areas of this anatomical set of the DMN are highly reproducible with different approaches, such as task-induced deactivation and functional connectivity. While the MTLs are part of the DMN regardless of which approach is used, relative to the robust posterior and anterior midline structures, the MTLs are less prominent using the approach of task-induced deactivations (Buckner, Andrews-Hanna et al. 2008). In fact, an ongoing research question is whether the hippocampus itself is part of the DMN or whether its membership is mediated by connections of the surrounding structures, such as the PHC (Ward, Schultz et al. 2013).

Figure 1.1: Early Summary of Deactivations within DMN Regions
Axial sections showing the DMN as a map of deactivations (a lighter colour towards red indicates greater deactivation) in a seminal meta-analysis of 9 PET studies. Reproduced with permission (Shulman, Fiez et al. 1997).
Important insights into the structural organization of the DMN have been provided by comparative studies in monkeys. For example, functional connectivity analyses of resting state fMRI in anaesthetised monkeys revealed that DMN connectivity transcends consciousness (Vincent, Patel et al. 2007). Further, structural connectivity analysis in monkeys suggests that the DMN includes multiple, distinct association areas, each of which is connected to other regions within the network (Buckner, Andrews-Hanna et al. 2008). That is, the posteriomedial cortex, including the PCC, RSP, and precuneus form the major hub of the posterior extent of the DMN. This complex has reciprocal connections to the MTLs, IPLs, and amPFC (Kobayashi and Amaral 2003; Kobayashi and Amaral 2007). The amPFC, the second major hub of the DMN, again shows reciprocal connections with the PCC, RSP, LTC, and MTL (Kondo, Saleem et al. 2003; Kondo, Saleem et al. 2005). These connectivity patterns match closely to the regions involved in the DMN. In humans, although lacking the direct anatomical evidence, DTI and structural MRI studies show a great overlap between structural and functional connectivity of the DMN (Hagmann, Cammoun et al. 2008; Horn, Ostwald et al. 2013; Hosseini and Kesler 2013). Further evidence of the strong cross-connectivity of the DMN in humans stems from EEG recordings, indicating a distinct neuronal signature of the DMN (Mantini, Perrucci et al. 2007). On a neuronal population level, using intracranial EEG in patients with drug-resistant medial temporal lobe epilepsy, DMN regions such as the PCC and amPFC show increased local neuronal activity at rest in comparison to an externally driven task, therefore providing a link between cell population activity and BOLD signal fluctuations (Miller, Weaver et al. 2009).

In relation to the neurocognitive networks defined above (see 1.2.2.2), the DMN appears to be unique in its centrality in the human brain. That is, rather than being one coherent network, the DMN appears to consist of a collection of hubs. For example, the DMN is closely overlapping with the structural core described above 1.2.2.1 and most of its nodes are also part of the rich club of the brain (van den Heuvel and Sporns 2011). Regions of the DMN mature together (Dosenbach, Nardos et al. 2010; Damaraju, Caprihan et al. 2013), have the highest aerobic glycolysis (Vaishnavi, Vlassenko et al. 2010), and simulated damage to any one of its cortical regions (i.e., there were no subcortical structures in the model) results in wide-spread functional connectivity changes (Alstott, Breakspear et al. 2009). As will be apparent in this thesis, the popularity of the DMN also results from studies indicating its promise of clinical relevance. For example, DMN connectivity alterations have been reported in numerous neurological and
psychiatric diseases, such as Alzheimer's disease (Buckner, Sepulcre et al. 2009), mTLE (Bernhardt, Hong et al. 2013), depression (Greicius, Flores et al. 2007) and schizophrenia (Whitfield-Gabrieli, Thermenos et al. 2009). Whereas this research stresses alterations in resting-state functional connectivity, another line of research focuses on the level of attenuation during goal-directed tasks and its relation to cognitive function (Miller, Celone et al. 2008). An optimistic perspective is that alterations of DMN, whether its functional connectivity or level of attenuation during externally-directed tasks, might provide ultimately a clinical diagnostic tool for these diseases (Zhang and Raichle 2010).

1.2.2.3.2 Role of the DMN in Active Cognition

While historically, DMN research focused on the network’s attenuation during most active tasks, it may also play a central role in active cognition. A current prominent hypothesis of DMN function suggests that the DMN enables construction of mental models or simulations that are adaptive and facilitate future behavior (Buckner 2012). By this view, the DMN operates mainly in internally-focused cognition that relies heavily on mnemonic systems. This hypothesis is supported by a number of observations stemming from memory research and will be discussed in greater detail below (see 1.3.2.1). To preview, the DMN may be used actively when AMs are retrieved, future events imagined (Addis, Wong et al. 2007) and other self-referential thoughts, for example, such as those evoked in theory-of-mind tasks (Saxe and Kanwisher 2003). Whereas the description of the DMN above as the structural and functional core of the human brain creates the image of one coherent network, recent DMN analyses focus on the important question whether the DMN can be fractionated into subnetworks. That is, various roles for DMN components have been suggested for scene construction (Hassabis and Maguire 2009; Vann, Aggleton et al. 2009), conceptual processing (Binder, Desai et al. 2009), self-referential or affective cognition (Gusnard, Akbudak et al. 2001), future-oriented thoughts (Addis, Wong et al. 2007), and semantic and episodic memory (Shapira-Lichter, Oren et al. 2013). Together with its estimated structural connectivity, these different viewpoints suggest that the DMN likely comprises multiple interacting subsystems (Laird, Eickhoff et al. 2009; Uddin, Kelly et al. 2009; Andrews-Hanna, Reidler et al. 2010). In fact, graph analytic measures and anticorrelated networks extracted of resting state fMRI indicated that the PCC and amPFC might constitute the hub regions within the DMN. Further, two subsystems of the remaining nodes emerged that correlated with the core midline but not with each other, these being the MTL and the dmPFC.
subsystems (Andrews-Hanna, Reidler et al. 2010). Importantly, targeted experimental manipulations then demonstrated different cognitive functions of each subsystem. The midline core (PCC and amPFC) was more active when people made self-relevant, affective decisions. The MTL subsystem, comprising the hippocampus, PHC, RSP, ventromedial PFC (vmPFC), and IPL became engaged when participants had to make decisions which involved constructing a mental scene concerning future events. In contrast, the dmPFC subsystem, comprising the dmPFC, temporoparietal junction (TPJ), LTC, and temporal pole (TempP) was preferentially activated when participants considered their present mental states (Andrews-Hanna, Reidler et al. 2010).

1.2.2.3.3 Role of the DMN in Brain Dynamics

Another prominent perspective describes that resting state networks are more appropriately linked to an inner state of exploration, in which the brain generates predictions about the likely network configuration that would be optimal for a given impending input (Deco, Jirsa et al. 2011). According to this proposal, resting state patterns are generated within a framework that is constrained by the underlying structural architecture but, around the same anatomical skeleton, a wide range of functional network constellations are being explored. For example, functional connectivity, measured over longer time scales, reflects the underlying anatomical architecture, such as the DMN. However, shorter time scales emphasize small departures from this pattern and numerous subnetwork configurations become visible (Honey, Kotter et al. 2007). Further, computational simulations revealed that these explorations of subnetworks emerge because the brain appears to be in a nonlinear, metastable state, on the edge of either continued or no oscillatory activity (Ghosh, Rho et al. 2008; Deco, Jirsa et al. 2009). In this metastable state, variability in physiological signals or “brain noise” facilitates the transition from one network to another network configuration, thus enabling the system to explore multiple states. These observations are commonly expressed in phase-plane plots and highlight the crucial link between space and time, such that functional connectivity patterns derived at one point in time might greatly differ from the spatial patterns seen at a different time point, assuming adequate sensitivity of the measuring technology. In sum, whereas the DMN stands out in its functional and structural coherence, and its centrality in the human brain, at any given point the precise functional configuration of even this network depends in part of the dynamic repertoire that is being explored and the impact of the current environmental demands.
1.2.2.4 Dynamical Patterns of Connectivity: Neuronal Context

The intricate anatomical connectivity of the human brain provides the basis for an enormous repertoire of possible functional network states. That is, given a fixed number of nodes and connections, the way these nodes and connections can be interconnected shapes the functional dynamics that can emerge. These dynamics, whether on the level of individual neurons or within and between neurocognitive networks, underlie information processing and computation that represent and encode important features of the internal and external world. The notion that cognition results from integrative operations throughout these levels, including large-scale brain networks, is a timely topic of investigation. Most prominently at the large scale, fMRI allows measuring simultaneous, distributed brain activity that can be related to cognitive processes (Bressler 1995; Deco, Jirsa et al. 2011). A critical aspect of brain function is therefore the examination of the neuronal context which is defined as the local processing environment of a given neuronal element that is created by the modulatory influences from other neuronal elements (McIntosh 1999). The idea of the neuronal context allows for the response properties of one network element to be profoundly affected by the status of other neuronal elements in that network. As a result, the relevance of a given neuronal element for cognitive function typically depends on the status of other interacting elements. By this definition, the processing performed by a given brain area may be modulated by a potentially large number of other areas with which it is connected. In that sense, the specialized function of any local cortical region depends on its topological uniqueness; that is, its particular set of interconnectedness or “connectional fingerprint” with other regions (Passingham, Stephan et al. 2002).

As will be apparent in this thesis, the exploration of the neuronal context of nodes within neurocognitive networks demands special attention. Whereas resting state fMRI connectivity suggests five or six major neurocognitive networks, the idea of the neuronal context suggests that each brain region’s possible functional interactions depend on its connectional fingerprints exceeding that of the major neurocognitive networks. For example, the contribution of the MTLs, part of the DMN, to learning with awareness is supported by a set of connected brain regions that is dissociable from MTL contributions to learning without awareness (McIntosh, Rajah et al. 2003). Importantly, the neuronal context of the MTLs exceeds the typical regions of the DMN, suggesting that individual brain regions have a far broader spectrum of possible functional interactions than the five major neurocognitive networks described above.
Another area of considerable interest is the identification of functional hubs; that is brain regions that occupy a central position within functional brain networks. As reviewed above, several prominent parts of the cerebral cortex, particularly along the cortical midline were identified as being widely and centrally functionally and structurally connected. Especially the PCC has been suggested as the functional and structural hub of the brain (Fransson and Marrelec 2008; Hagmann, Cammoun et al. 2008; Buckner, Sepulcre et al. 2009; van den Heuvel and Sporns 2011). In the discussion of the neuronal context idea, it is interesting that the PCC displays a complex and dynamic pattern that partially reflects activity in other brain networks (Leech, Braga et al. 2012). For example, ventral subregions of the PCC are strongly connected to the DMN, whereas dorsal subregions show strong connections to the fronto-parietal attention network. This evidence suggests that the PCC acts as a functional integration hub for various cognitive tasks.

1.2.3 Summary

Brain networks can be explored on all levels, from the microscale of molecules and synapses to the macroscale of interacting large-scale neurocognitive networks. A major distinction can be made between structural connectivity which refers to the actual physical link between two neuronal elements and functional connectivity which refers to statistical dependencies between measured time series recordings. The most frequently used techniques to measure brain connectivity in humans are DTI and fMRI as they allow examining large-scale neurocognitive networks in vivo.

Together, structural and functional connectivity research revealed that the brain is organized according to a small world architecture in which neighbouring regions are more densely connected than regions further apart. Within this small world configuration, a distinct set of brain regions, commonly called the Default Mode Network (DMN) appears to constitute the core network of the human brain. That is, regions within the DMN, including the PCC and the amPFC, lateral parietal cortices and the MTLs, display high degree and centrality, and are part of the so called brain’s rich club. Further, functional connectivity measured over a longer period of time, such as typically seen in resting state experiments, reflects mostly the underlying structural connectivity. However, functional connectivity measured at shorter intervals, such as during experimental tasks, emphasizes the dynamical repertoire of the individual regions. Accordingly,
the neuronal context idea provides a framework to set network interactions into a dynamical and fast evolving perspective. Here, subnetworks of the DMN that are formed transiently support distinct cognitive tasks and even further, individual nodes of the DMN have been shown to display a rich dynamical repertoire of possible functional interactions with brain regions outside the DMN.

1.3 Networks of the Medial Temporal Lobe underlying Episodic Memory

The network characteristics described above can be illustrated by exploring the network setting of the MTL. A long standing history of brain research indicates that the MTL supports episodic memory, our ability to mentally re-experience past events. In fact, the MTL has been demonstrated as a functionally highly specialized brain region and critical node in the episodic memory domain. The MTL is further a rich club member and part of the DMN. The next section will first review research focusing on the MTL and then explore how the MTL interacts with regions of the DMN and non-DMN regions to support episodic memory function.

1.3.1 The Medial Temporal Lobes and Episodic Memory

The first descriptions of episodic memory as a distinct memory system in the human brain was closely related to a tragic outcome of a surgical intervention performed on August 25, 1953. At that time, the neurosurgeon Scoville surgically removed both MTLs, including the anterior two thirds of the hippocampi, most of the amgydalae, and entorhinal cortices from the patient Henry G. Molaison, H.M., in the attempt to eliminate recurrent epileptic seizures (Scoville and Milner 1957; Corkin, Amaral et al. 1997). Whereas the amount of epileptic seizures did decrease after the surgery, the removal of both MTL structures resulted in severe memory loss. In the following 50 years of his life, numerous research studies focusing on the patient H.M. revealed fundamental insights into the nature of human memory (Corkin 2002; Annese, Schenker-Ahmed et al. 2014). Two cases with amnesia following unilateral MTL resection with suspected (and in one case afterwards confirmed) contralateral MTL damage were reported before Scoville’s
surgical intervention (Milner and Penfield 1955; Penfield and Milner 1958), however, the knowledge about the precise location of the lesion together with an otherwise intact brain, and H.M.’s preserved intellect, made him to perhaps the most famous patient in the field of neuropsychology.

Landmark studies on H.M. revealed that, due to his surgery, he had lost the ability to form, consolidate and retrieve long-term memories (Scoville and Milner 1957). Initially, his profound impairment to retrieve AMs were thought to extend back for around 10 years but based on improved interview strategies (Levine, Svoboda et al. 2002), it became clear that these early findings underestimated his impairment. H.M. was severely impaired on AM tasks with no temporal gradient (Steinvorth, Levine et al. 2005), demonstrating a severe retrograde amnesia for event details. In contrast to this loss of already established AMs, H.M. could remember facts about the world, such as famous people or events that he learned before his surgery. (Corkin 2002). Further, although he could perceive and encode information normally, he was unable to hold on to this information for more than about 30 seconds without active rehearsal. Most strikingly, H.M. could learn new motor skills, such as the mirror-tracing task. Based on the careful exploration of H.M.’s impaired and spared cognitive abilities, the field of neuropsychology began to distinguish between memory systems that were dependent, such as the ability to remember specific episodes of his life, and independent, such as implicit motor learning, on the MTL. The process of tying specific memory processes to distinct brain regions revolutionized the neuropsychology of human memory processes.

Since then, much work has been done to describe this brain-behavior relationship and some of the early interpretations have been challenged and modified. For example, Tulving (1983) proposed a formal distinction between memories that are specific in time and place which he termed episodic memories and semantic memories that comprise general facts. In contrast to MTL-dependent episodic memory, semantic memory does not depend on the MTL as was shown by H.M.’s preserved presurgical semantic knowledge (Corkin 2002). The construct of episodic memory entails the ability to travel mentally through subjective time, from the past to the future, thus allowing one to re-experience, one’s own previous and imagined experience (Tulving 1973; Tulving 2002). Tulving refers to the special consciousness that allows being aware of this subjective time travel as autonoetic consciousness. The essence of episodic memory lies therefore in the conjunction of three concepts, self, autonoetic awareness and subjectively sensed
time. In this sense, AM retrieval can be seen as the heart of episodic memory and H.M. dramatically showed that the ability to retrieve AMs depends on the MTL (Scoville and Milner 1957; Steinworth, Levine et al. 2005). However, the retrieval of autobiographical and other episodic memories extends beyond functions of the MTL (Conway and Pleydell-Pearce 2000; Greenberg and Rubin 2003), depending on interacting distributed brain regions supporting for example semantic memory and self-referential processes. As described in more detail in section 1.3.2.1, autobiographical and episodic memory is supported by a distributed wide-spread network that overlaps with but also extends beyond the networks subserving semantic memory (Addis, McIntosh et al. 2004; Burianova and Grady 2007; Burianova, McIntosh et al. 2010).

1.3.1.1 Anatomical Organization of the MTL

Whereas the removal of several MTL regions in H.M. made it difficult to pinpoint functional dissociations between these regions, other patients, animal models and recent advances in fMRI have unraveled distinct functional components of the MTL that closely follow its anatomical organization (see Figure 1.2). The anatomical organization of the major pathways of interactions between the neocortex and the MTLs, as well as the organization of the MTLs themselves, is largely conserved across mammalian species from rodents to primates (Suzuki and Amaral 1994; Eichenbaum 2000; Dickerson and Eichenbaum 2010). In both rats and monkeys, virtually all neocortical association areas send projections that converge onto hippocampal adjacent cortical areas, including the perirhinal cortex, PHC, and the entorhinal cortex. These structures then project onto specific subdivision of the hippocampus, thus serving as a convergence site for cortical input mediating the distribution of cortical afferents to the hippocampus. The hippocampal subdivisions are internally connected via unidirectional pathways, starting with the dentate gyrus, and continuing through CA3, then CA1, and then the subiculum. This internal hippocampal organization is commonly referred to as the trisynaptic loop. Along the longitudinal axis, these trisynaptic loops are organized in lamellar formation and heavily interconnected via longitudinal association fibres (Amaral and Witter 1989; Sloviter and Lomo 2012). The cortical outputs of hippocampal processing, arising in CA1 and subiculum, involve feedback connections back to the PHC which projects back to the neocortical association regions from which the inputs to the MTL originated.
The anatomical connectivity of the MTL, together with a substantial body of evidence on the selective damage to these areas and fMRI suggests functional dissociations between MTL subregions which will be reviewed in the next section.

1.3.1.2 Functional Organization of the MTL

Despite substantial efforts to characterize the functional organization of the MTL, no general consensus has been reached so far. A complete review of the material available on this topic would go far beyond the scope of this literature review. Therefore, one prominent approach, the Binding in Context (BIC) model (Eichenbaum, Yonelinas et al. 2007; Ranganath 2010) will be reviewed with some relation to other important ideas. In this framework, perirhinal cortex and PHC play different roles in memory based on their dissociable anatomical connectivity. Extrapolating from aspects of MTL connectivity, the perirhinal cortex may process information about specific items, such as who and what, and the PHC may process information about the context, such as when and where. The role of the hippocampus is then to bind information between items and context. This model builds on the idea that the perirhinal cortex is sufficient to support item recognition based on familiarity, whereas the hippocampus supports recall or recognition based on conscious recollection. Recollection, at the heart of episodic memory, describes a subjective phenomenon which gives rise to the conscious experience of remembering. In contrast, familiarity in the absence of recollection gives rise to the subjective feeling of knowing (Tulving 1985; Yonelinas 2002). In agreement, patients with hippocampal damage have selective recollection deficits while leaving familiarity mainly spared (Moscovitch and McAndrews 2002; Bastin, Linden et al. 2004; Quamme, Yonelinas et al. 2004; Tsivilis, Vann et al. 2008). An important piece to the double dissociation between hippocampal and perirhinal contributions to recognition memory was found in the patient N.B. who revealed impaired familiarity with spared recollection after anterior temporal lobe resection that included a large portion of her perirhinal cortex but spared her hippocampus (Bowles, Crupi et al. 2007). Functional imaging studies further illustrated the functional dissociation between MTL regions. A number of different measures can be used to disentangle recollection and familiarity, including remember/know, recognition confidence, or item and source recognition paradigms (Yonelinas 2002). Results of a review from over 20 fMRI studies revealed increased hippocampal activity in studies targeting recollection during both encoding and retrieval (Diana, Yonelinas et al. 2007). Even further subdividing the processes of the hippocampus, recent data support the functional
dissociation between anterior and posterior segments of the hippocampus (Poppenk and Moscovitch 2011; Poppenk, Evensmoen et al. 2013). That is, the anterior hippocampus might support coarse, global information of associations, whereas the posterior hippocampus might support fine-grained, local associations. For example, Poppenk (2013) speculates that during AM retrieval, the anterior hippocampus supports associative binding between main actors and story settings, whereas the posterior hippocampus supports the retrieval of the exact spatiotemporal characteristics of the event.

In support of the BIC model, imaging studies have further distinguished between functional roles of perirhinal cortex and PHC. Encoding and retrieval activation in the perirhinal cortex has been correlated with item familiarity and with successful recollection of details about specific entities, whereas activation in the PHC is increased during successful encoding and retrieval of contextual associations with these items. Differences in the recruitment of these regions have been attributed to different types of stimuli that is being processed, such as objects versus scenes (Mullally and Maguire 2011), or the underlying representational characteristics, such as item versus context information (Diana, Yonelinas et al. 2007).

The functional organization of the MTL was brought into the focus of research though the profound loss of mnemonic abilities that arise with damage to this brain region. However, more recent ideas, like the BIC model outlined above, have begun to examine MTL involvement in processes beyond long-term memory. The general idea is that a specific brain region, rather than supporting only one cognitive construct, such as episodic memory, contributes a specific process to cognitive function. According to the BIC model for example, the hippocampus binds items into their context, regardless whether it is doing so during encoding and retrieval of long-term (Diana, Yonelinas et al. 2007), short-term memory (Stern, Sherman et al. 2001; Hasselmo and Stern 2006; Olsen, Nichols et al. 2009) or even perceptual tasks (Murray, Bussey et al. 2007).

In sum, cases like the patient H.M. demonstrated that the hippocampus is critical for associative binding of multiple details that enables one to mentally re-experience an autobiographical event. However, the vivid mental imagery that accompanies recollection clearly depends on brain wide interactions with the hippocampus. As will become apparent, especially the interaction between the hippocampus and regions of the DMN seem important for recollection. Nonetheless, as the neuronal context idea might predict, the fine grain spatiotemporal connectivity pattern of
hippocampal-neocortical interactions might ultimately reflect which cognitive task is currently supported. The next section will take a closer look at the hippocampus in its brain wide neuronal context.

1.3.2 Hippocampal-Neocortical Network Interactions

The main neocortical association areas that project to the MTL consist of the PCC, RSP, lateral parietal cortices and amPFC which overlap significantly with the DMN (Eichenbaum 2000; Dickerson and Eichenbaum 2010). Whereas these neocortical areas differ considerably between the rat, monkey and human brain in terms of cortical size and laminar stratification, the general organization of pathways and interaction with the MTL is remarkably similar between these species (see Figure 1.2). This characterization of anatomical organization of a hippocampal-neocortical dialogue, together with the discovery of synaptic changes due to long-term potentiation and the specific neuropsychological profile of H.M., led to the formation of the so called index theory (Teyler and DiScenna 1986; Teyler and Rudy 2007). According to this framework, representations of complex life events are indexed throughout a neocortical hierarchical indexing scheme. That is, relatively simple features of episodic memories are represented in specific primary sensory neocortical areas and more complex conjunctions of these features are then indexed by supplementary and subsequently association cortices. Then, neocortical association areas, representing multimodal information about an episode, then project to the hippocampal surrounding cortices, mostly to the entorhinal cortex which in turns projects to subregions of the hippocampus. As a consequence, synapses connecting co-activated intrahippocampal and entorhinal-hippocampal neurons are strengthened. The outcome of this hippocampal-entorhinal-neocortical interaction is thought to represent the memory trace. Therefore, this theory assumes that the experience itself is represented as a set of strengthened synapses in the hippocampus; whereas there are no modifications among neocortical neurons. Thus, the memory trace is a hippocampal representation of co-occurring patterns of activity in the neocortex. The indexing nature of the memory trace can be illustrated in relationship to memory retrieval. During memory retrieval, a subset of the original neocortical pattern is re-activated. The projections from these input patterns activate the connected neurons in the hippocampus representing the original episode. The activation of this representation then projects back to the neocortex to activate the pattern representing the entire experience. In this framework, the hippocampus itself does not contain any content but an index that allows the
content to be reinstated. Oscillatory brain rhythms, such as theta oscillations might orchestrate this complex hippocampal-neocortical interplay (Duzel, Penny et al. 2010; Fell and Axmacher 2011; Fuentemilla, Barnes et al. 2014).

Whereas the index theory focuses mostly on hippocampal-neocortical interactions during encoding and retrieval, the Multiple Trace Theory summarizes data regarding memory consolidation (Nadel and Moscovitch 1997). Here, each time a memory is retrieved, it is re-encoded automatically by the hippocampus along with its new context in which retrieval occurred. The more often a memory is retrieved, the more traces there are and the more opportunities for overlapping, partial neocortical activation patterns there are that lead again to re-encoding of the memory. Detail-rich, episodic memories depend on the intact dialogue between neocortex and hippocampus no matter how old these memories are because the hippocampal index is the only link that can re-activate the original pattern of neocortical activation (Nadel and Moscovitch 1997; Moscovitch, Rosenbaum et al. 2005). However, over time and experience, the re-encoding of memories along with their updated context triggers neocortical plasticity in that neurons in the neocortex develop a schematic version of the original memory which contains some of its essential features and meaning but few of its contextual details. More recently, it has become clear that memories that were initially dependent on the hippocampus are fundamentally different from those represented ultimately in the neocortex (Winocur, Moscovitch et al. 2010; Winocur and Moscovitch 2011). Whereas hippocampal-dependent memories are detail-rich and most often specific in time and place, neocortical memories lack the specific detail and represent schematic information. Over the past decade, a large body of empirical work has converged on the proposition that retrieval of certain types of detail from remote AMs remains dependent on hippocampal engagement (Moscovitch, Rosenbaum et al. 2005; Winocur, Moscovitch et al. 2007; Goshen, Brodsky et al. 2011). Much less is known about hippocampal-neocortical interactions during episodic retrieval, however, recent research points towards important roles of many of the regions within the DMN (Rugg and Vilberg 2013).
1.3.2.1 Default Mode Network in Action

As described above, the main association cortices that project to the MTL overlap substantially with the DMN. Whereas section 1.2.2.3 describes structural and functional properties of the DMN as a resting state network, this section will review the same regions during active cognition (see Figure 1.2).

**Figure 1.2: Hippocampal-Neocortical Connectivity and Relation to the DMN**

Panel A indicates the main anatomical connections between the hippocampus and neocortex in the primate (left) and the rodent (right), reproduced with permission from (Eichenbaum 2000). Panel B displays the results of an ALE meta-analysis of fMRI studies examining autobiographical memory (turquoise), navigation (purple), theory of mind (dark blue), and DMN (green). Red and yellow indicate the conjunction between two and three domains, respectively. Reproduced with permission from (Spreng, Mar et al. 2009). Panel C illustrates the regions implicated in a general recollection network. Reproduced with permission from (Rugg and Vilberg 2013).
In addition to increased hippocampal and parahippocampal activity, successful remembering of episodic material is characteristically associated with increased activity in a set of cortical regions that include the PCC, RSP, IPL centered on the angular gyrus, and the amPFC. Because of the density of its connections with the hippocampus and the memory impairments that accompany lesions to these regions, this co-activation pattern has recently been suggested as a general recollection network (Rugg and Vilberg 2013). The robustness of these co-activation patterns across a wide variety of test materials and procedures for operationalizing recollection processes have led to the proposal that these regions constitute a general network engaged when a retrieval cue elicits recollection. In agreement with this proposal, vivid detail-rich AM retrieval, at the heart of the subjective feeling of recollection, elicits the same neocortical co-activation pattern as recollection of experimental stimuli (Maguire 2001; Svoboda, McKinnon et al. 2006). Interestingly, imagining future events (Addis, Wong et al. 2007) and the thoughts and feelings of others, as in so called theory of mind tasks (Saxe and Kanwisher 2003) also cause this co-activation pattern (Spreng and Grady 2010). At a closer look, even familiarity effects are present in the parahippocampal gyrus, retrosplenial cortex/PCC and the left angular gyrus (Hayama, Vilberg et al. 2012). Together, these latter findings suggest that this MTL co-activation pattern support processes that extent beyond the subjective feeling of recollection. Here again, it seems likely that, rather than supporting only one subjective phenomenon, these regions can re-assemble dynamically into subnetworks that support various aspects of human cognition, such as planning the future or reminiscing in the past. As described below, in agreement with this, a change in the strength or direction of connectivity between the same brain regions might support different cognitive processes (McCormick, Moscovitch et al. 2010). Drawing on ideas from network analysis, the MTL can be seen as a critical node in the neurocognitive networks supporting episodic memory function (see 1.3.1). In contrast, the other neocortical regions can be seen as ancillary nodes in that damage to each one of these regions does have a distinguishable negative impact on episodic memory function but does not result in such a drastic antero- and retrograde amnesia seen with bilateral MTL damage. From that perspective, each node provides a unique contribution which as an interacting system supports episodic memory function.
1.3.2.1.1 PCC/RSP Contributions to Episodic Memory

Anatomically, the RSP cortex (BA 29 and 30) is linked reciprocally to the hippocampus, PHC, medial PFC and PCC (Greicius, Supekar et al. 2009). Generally, neuropsychological explorations of the human RSP cortex are problematic because of the difficulties in isolating this area. Nevertheless, the rare findings from RSP cortex lesions in humans suggest an important contribution to spatial navigation and episodic/autobiographical memory (Vann, Aggleton et al. 2009). These aspects are further supported by fMRI studies revealing a key role of the RSP cortex in scene construction, i.e., the mental process of generating and manipulating a complex coherent scene. This process may underpin functions such as AM, navigation and thinking about the future (Vann, Aggleton et al. 2009).

Activation of the PCC occurs in a variety of introspective cognitive tasks, such as episodic and semantic memory retrieval but also interoception and emotion (Binder, Desai et al. 2009; Laird, Eickhoff et al. 2009). For example, the PCC is one of the few brain regions in which activation during AM retrieval and retrieval of laboratory episodic memories overlap (McDermott, Szpunar et al. 2009). On the other hand, reliable decreases in activation are found during goal-directed tasks, such as episodic memory encoding (Daselaar, Prince et al. 2004; Laird, Eickhoff et al. 2009). Because of its involvement in this broad array of cognitive tasks, the PCC has been suggested as the main hub of the brain, integrating information from various large-scale systems (Fransson and Marrelec 2008; Pearson, Heilbronner et al. 2011; Leech, Braga et al. 2012). For example, Leech et al. (2012) found distinct subregions in the PCC which reflected activation in different neurocognitive networks. Therefore, one account suggests that during episodic memory, the PCC integrates specific episodic information with other ongoing perceptual, semantic, affective, and motor representations.

1.3.2.1.2 PFC Contributions to Episodic Memory

The important role of the PFC to episodic memory retrieval is widely established (Conway, Pleydell-Pearce et al. 2001; Maguire 2001). In fact, early theories about the hippocampal-neocortical interactions stress the importance of the PFCs to enable a flexible manipulation of remembered materials (Moscovitch 1995). Since then, the contributions of subregions within PFC to episodic memory retrieval have been articulated. For example, the medial portion of the PFC (BA 9 and 10) is one of the most commonly reported brain regions of MTL co-activation
during AM retrieval, a hub of the DMN, and it has been suggested to be crucial for self-referential or internally focused processes (Svoboda, McKinnon et al. 2006; Abraham 2013). Other regions of the PFC, such as the vmPFC are currently considered to support the formation or coordination of schemas which describes a semantic knowledge structure (van Kesteren, Ruiter et al. 2012; Ghosh and Gilboa 2013; Preston and Eichenbaum 2013). In contrast, the dmPFC might support the self-guided retrieval of semantic knowledge (Binder, Desai et al. 2009). Finally, ventrolateral (vIPFC) and dorsolateral (dIPFC) PFC activation has been attributed to support the reconstruction of AM, that is strategic retrieval, verification and selection of information from posterior cortical association cortices (Svoboda, McKinnon et al. 2006).

1.3.2.1.3 Lateral Parietal Cortex Contributions to Episodic Memory

The lateral parietal cortex has long been known to support attention during perception and representation of location (Bisiach and Luzzatti 1978) but has only recently been implicated in episodic memory (Davidson, Anaki et al. 2008; Vilberg and Rugg 2008; Vilberg and Rugg 2009; Vilberg and Rugg 2009). Paralleling its role in perception, a neurocognitive model suggests that MTL mechanisms underlying recollection processes may capture attention processes supported by the IPL (Cabeza, Ciaramelli et al. 2008). This attention allocation in turn might enable the conscious reflection on episodic memory material. In agreement with this proposal, damage to this brain region leads to deficits with respect to self-initiated retrieval of AMs (Berryhill, Phuong et al. 2007) and in the proportion of items recollected rather than direct impact on the accuracy of recognition memory (Ally, Simons et al. 2008; Davidson, Anaki et al. 2008; Simons, Peers et al. 2008; Simons, Peers et al. 2010).

1.3.2.1.4 Lateral Temporal Cortex Contributions to Episodic Memory

Lastly, the LTC extending into the TempP has been suggested to be part of the general recollection network (Rugg and Vilberg 2013). Largely based on fMRI and computational models, these brain regions in the human brain are most likely involved in multimodal information integration and concept retrieval (McClelland and Rogers 2003; Binder, Desai et al. 2009). Damage to bilateral LTC and TempP, as occurs frequently in herpes simplex encephalitis, often result in profound semantic deficits (Warrington and Shallice 1984). Semantic dementia, the temporal lobe variant of the fronto-temporal dementia, is characterized by a progressive degeneration of the anterior ventrolateral temporal lobes, accompanied by a gradual loss of
semantic knowledge (Lambon Ralph, Lowe et al. 2007). Based on these findings, the LTC and TempP have been suggested as the storage site of perceptual information about objects and their schematic attributes (Binder, Desai et al. 2009).

This brief review of the variety of cognitive processes supported by the typical MTL co-activation partners illustrates clearly that there are many interacting but distinct cognitive functions involved in retrieving an episodic memory. It also suggests strongly that this network is not a fixed unit but can be re-assembled dynamically to support current task demands. Further drawing on the neuronal context idea, it will become apparent in the next section that the MTL can flexibly interact with virtually all brain regions, not just its typical partners reviewed above.

1.3.2.2 Flexible Networks supporting Episodic Memory

In line with the current proposal, it is neither new nor surprising that the brain does not strictly follow the distinction between multiple memory systems neatly described by behavioral psychologists. Nonetheless, careful designed experiments with patients and improving functional neuroimaging techniques over the last decades have contributed to illuminate that there are several different memory systems in the brain. One prominent account summarizes that these systems are comprised of different memory processing components which can be associated with different brain regions (Moscovitch 1992). These components or brain regions are recruited in different combinations by memory tasks, yielding complex patterns of transient associations and dissociations. Some components may be specific to tasks traditionally associated with one memory system, but other components are shared by tasks attributed to different memory or even non-memory systems, such as attention and perception. This perspective acknowledges the functional specialization (Friston 1994) of a given brain region but does so on a neuronal process rather than a psychological systems level. For example, the hippocampus might be involved in binding processes no matter whether this processing unit is employed by a mnemonic or perceptual task (Olsen, Moses et al. 2012). While generally in agreement with the neuronal context idea (McIntosh 1999), the component process framework highlights the functional importance of a few key interacting neuronal elements, called process specific alliances, to support a specific cognitive function, rather than the importance of the global state of a network (Cabeza and Moscovitch 2013).
Drawing on the idea of the component processes, the theory that the hippocampus is involved in the process of binding complex items into context can account for its activation during implicit memory (Henke, Treyer et al. 2003; Henke 2010) and perceptual tasks as long as there is an relational component necessary (Olsen, Moses et al. 2012). Likewise, the theory that the perirhinal cortex is involved in the process of integrating perceptual features can explain its activation during perceptual tasks even without any memory component (Barense, Groen et al. 2012). A central prediction of this model would be that although the same region can be activated during two different cognitive tasks, such as memory and perception, its connectivity pattern during those tasks should be distinguishable. Indeed, functional neuroimaging supports this hypothesis (McIntosh, Rajah et al. 2003; McCormick, Moscovitch et al. 2010; O’Neil, Protzner et al. 2012). For example, the same region of the hippocampus signaled differential activation for encoding and retrieval of recollected versus familiar faces (McCormick, Moscovitch et al. 2010). Functional connectivity analyses then revealed that this hippocampal region interacted with the same neocortical regions during both encoding and retrieval. However, a subsequent effective connectivity analysis revealed distinguishable connectivity patterns, with causal influences proceeding in opposite directions, for encoding and retrieval within this hippocampal-neocortical dialogue. Another example indicated distinguishable functional connectivity patterns of hippocampal-neocortical interactions during AM retrieval (Sheldon and Levine 2013). Here, the same connectivity pattern was found to support recent and remote AM retrieval as long as it remained a vivid mental image, whereas faint memories were supported by a different network. And lastly, a carefully designed experiment showed that both complex perceptual and mnemonic tasks activated the perirhinal cortex but that functional and effective neocortical connectivity patterns differed between those two conditions (O’Neil, Protzner et al. 2012).

An important detail to notice from these studies is that the hippocampus frequently forms transient relationships with brain regions outside its typical partners (see 1.3.2.1). This evidence suggests that the regions commonly co-activated with the MTL constitute a general network supporting a wide variety of cognitive processes, such as detail-rich retrieval or contextual binding. However, insight into flexible network dynamics also underlines that process specific alliances can be very specific to support distinct cognitive tasks, such as relational face memory and face perception. In other words, if averaged over a variety of relational processing tasks, the
MTL might show strong coupling with DMN regions, however looking at specific instances or a subset of these relational tasks, the MTL might be coupled to additional ancillary nodes to support the specific task demands.

1.3.3 Summary

It is well established that the hippocampus is critical for forming and retrieving vivid, detail-rich AMs. Through careful explorations of patients with MTL damage and more recently, functional neuroimaging, it has become evident that the hippocampus supports processes that involve binding of items or features of items in their context. Other MTL structures support processes leading up to the integrative hippocampal representation. In that sense, the MTL can be seen as a hierarchical network funneling information to the hippocampus. This MTL network can also be placed into a broader, brain wide network, describing interactions between the MTL and neocortex. Interestingly, a wide variety of different materials and experimental designs examining recollection recruits the same MTL co-activation patterns which significantly overlap with the DMN and for that matter reflect its anatomical connections to the rest of the brain. At a closer look, each of these MTL partners appears to contribute a unique process to the overall episodic memory function. It seems that the constant interactions between MTL and these regions provide the fundamental architecture to perform episodic memory tasks flawlessly. Nonetheless, the MTL can also form transient process-specific alliances beyond its typical partners, demonstrating its rich functional repertoire. Together, these lines of research strongly suggest that within the episodic memory domain, the hippocampus and adjacent MTL structures hold a hub function. This function might be best summarized as its capability to bring together general processes, such as attention but also specific processes fine tuned to the current task demands, for example, face perception.
1.4 Network Disruptions in Medial Temporal Lobe Epilepsy

Historically, studies examining patients with mTLE have produced major insights into MTL function and how damage to this brain region affects episodic memory. However, far less is known about how unilateral MTL damage affects the episodic memory networks outlined above. For example, how does damage to this region affect the DMN? Further, if the hippocampus is the central hub of flexibly changing episodic memory networks, how do those networks appear in patients with mTLE? And lastly, can network analysis help in the clinical setting of mTLE? The next section will concentrate on what is known about these questions.

1.4.1 Focusing on the MTL in mTLE

1.4.1.1 Clinical Description of mTLE

Epilepsy is a prevalent neurological disorder affecting an estimated 50 million people worldwide (Meyer, Dua et al. 2010). This disorder is defined by recurrent epileptic seizures of varying kinds and intensity (Fisher, van Emde Boas et al. 2005). However, people with epilepsy must further live with other devastating consequences impacting their quality of life, such as the fear of having another seizure, cognitive impairment, social stigma associated with seizures, driving inability, and higher rates of mortality and co-morbidities such as depression and anxiety. In fact, at the 2013 conference sponsored by the National Institutes of Neurological Diseases and Strokes (Curing the Epilepsies: Pathway forwards, www.ninds.nih.gov/research/epilepsyweb), the need to understand the adverse impact of seizures on quality of life and cognitive abilities were identified as major new benchmark areas for research. Further, the Ontario Brain Institute (OBI) recently identified epilepsy as a significant clinical burden for Canadians and funded a prestigious multi-site research project aiming to integrate discoveries around epilepsy from multiple disciplines including neuropsychology, computation, imaging, genetics and proteomics (http://www.braininstitute.ca). When asked directly, individuals with epilepsy identify cognitive problems, including memory problems, concentration difficulties, and the ability to think clearly as one of the most important complications associated with their disorder (Fisher, Vickrey et al. 2000).
Epilepsy itself can be divided into a number of syndromes determined by seizure type and EEG abnormalities. The clinical manifestation of a seizure depends critically on the localization of the origin but also on the speed and pattern of seizure spread. According to the recently renewed guidelines of the International League Against Epilepsy (ILAE), the main categorization of epilepsy is organized according to their electroclinical syndrome (Berg, Berkovic et al. 2010). The most common form of all focal epilepsies and the main focus of the current thesis is mTLE which is characterized by recurrent seizures originating from the hippocampus and surrounding cortices. The electroclinical syndrome of unilateral mTLE rests upon four characteristics: seizure semiology, EEG abnormalities, structural MTL abnormality, and neuropsychological profile (Berg, Berkovic et al. 2010). mTLE seizures usually lasts between one and five minutes in which consciousness is disturbed. The hallmarks of this type of seizures are initial auras in which the patient can experience déjà vu, déjà entendu, and other forms of memory recollections, followed by motor arrests, automatisms and frequently by secondary generalization of epileptic activity (Walker, Chan et al. 2007). Scalp EEG recordings usually demonstrate interictal epileptiform abnormalities, particularly spikes and sharp waves over the temporal region. During a seizure, these recordings reveal typically a slow sharp synchronous activity localized to the temporal region which commonly spreads to involve a larger field including the contralateral hemisphere. Structural MRI, to rule out other differential diagnosis and to search for a structural cause, is performed in most cases. The most common neuropathological lesion identified in patients with mTLE is medial temporal lobe sclerosis (MTS), which is characterized by GMV loss, specifically within the CA1 region, of the hippocampus and resultant gliosis in that tissue (Walker, Chan et al. 2007). Due to its importance to the current thesis, the neuropsychological profile will be explained in greater detail below (see 1.4.1.2) but to preview, most prominent are episodic memory deficits that relate usually to the affected side; verbal memory deficits if the left MTL and visuospatial memory deficits if the right MTL is dysfunctional.

There are many antiepileptic drugs available for seizure management, such as phenytoin, topiramate, valproat and phenobarbital (Patsalos, Berry et al. 2008). Nearly all antiepileptic drugs act by decreasing the excitation of neurons, either by down-regulating excitatory or by enhancing inhibitory neurons. Unfortunately, up to a third of patients with mTLE do not experience adequate seizure control with medication. For patients with intractable unilateral mTLE in whom EEG characteristics, seizure semiology, neuropsychological tests and neuroimaging are
concordant, resective surgery may result in seizure freedom (Wiebe, Blume et al. 2001). In cases where scalp EEG does not reveal a clear unilateral seizure onset focus, iEEG including hippocampal depth electrodes might serve as an additional localization diagnostic. A traditional anterior temporal lobe resection removes the anterior hippocampus, parahippocampal gyrus (including perirhinal, entorhinal and some PHC), amygdala, TempP and a variable extent of LTC (Penfield and Baldwin 1952; Wiebe, Blume et al. 2001). More selective forms of resections, such as the selective amygdalohippocampectomy, has recently been associated with a similar short-term seizure control compared to the traditional approach but with possibly a better cognitive outcome (Helmstaedter, Richter et al. 2008; Schramm 2008; Sherman, Wiebe et al. 2011).

1.4.1.2 Neuropsychological Profile of mTLE

Historically, the clinical care of epilepsy patients has made important contributions to the understanding of brain organization and human cognition (Loring 2010). For example, as early as 1930 the Canadian neurosurgeon Wilder G. Penfield who developed the Epilepsy Program at the Montreal Neurological Institute (MNI) performed stimulation language mapping to identify brain regions of eloquent cortex to help guide surgical resection (Penfield 1930). During this procedure, the patients were awake and encouraged to talk to Donald O. Hebb who also worked at the MNI at that time. Brenda Milner was a graduate student of Hebb in the 1950’s and he recommended to Penfield that she evaluate potential changes in his patients pre- to postsurgical. In early reports, Milner and Penfield noticed some cases of severe amnesia following unilateral MTL resections (Milner and Penfield 1955; Penfield and Milner 1958). They hypothesized that these patients had previous undetected lesions to the contralateral MTL and the effect of the unilateral MTL resection resulted essentially in bilateral MTL damage. Consistent with this proposal, the serious memory problems seen in H.M. (see 1.3.1) were published a few years later (Scoville and Milner 1957). They further noticed that unilateral MTL resection usually caused less severe memory deficits in a typical pattern depending on the affected hemisphere (Milner 1958; Penfield and Milner 1958). That is, Milner described material-specific memory difficulties, the clearest examples seen in left mTLE who showed a postoperative reduction in the ability to recall verbal but not visuospatial material. Correspondingly, although less clear, patients with right mTLE were selectively vulnerable to visuospatial material (Milner 1968). They noted that these deficits were generally greater with more substantial removal of the hippocampus and associated MTL cortices.
The influence of this early work was profound and served as a foundation for the cognitive neuroscience of memory. Since then, a tremendous amount of work has been done to refine the understanding of MTL function and studying patients with mTLE continues to play a key role in this investigation. Today, the clinical neuropsychological evaluation of patients with mTLE involves a variety of standardized tests examining multiple cognitive domains, such as intellectual abilities, attention, language, executive function, and memory (Jones-Gotman, Smith et al. 2010; McAndrews and Cohn 2012). As the MTLs are crucially involved in episodic memory it is not surprising that memory testing is at the core of the clinical assessment of patients with mTLE.

1.4.1.2.1 Material Specificity in mTLE

Up to today, the material-specific model of memory is used by clinical neuropsychologists as a presurgical guide whether the left or right MTL might be the epileptogenic focus (Helmstaedter and Elger 1996; Elger, Grunwald et al. 1997; Gleissner, Helmstaedter et al. 2002; Helmstaedter, Richter et al. 2008). In practice, the clinical neuropsychologist assesses scores from both verbal and visuospatial memory tests against a normative distribution and against each other. The presence of an asymmetry between these scores is then interpreted as sign of a material-specific deficit and provides clues on the lateralization of the dysfunction. Postsurgically, the material specific memory deficits tend to become more evident. That is, on average, verbal memory outcome is worse after left than after a right MTL resection, although many patients who undergo left MTL resection show no change or might even show improvement postsurgically. By contrast, patients undergoing right epilepsy surgery sometimes show an improvement in verbal memory but some also exhibit decline. Similar variability has been associated with visuospatial memory following right MTL resection with even less robust effects.

Therefore, additional concepts about MTL function, for example the dissociation between episodic and semantic memory have now been incorporated in standard neuropsychological evaluation of patients with mTLE. More recent models of MTL function, such as the BIC model described above (see 1.3.1.2), are currently explored in patients with mTLE but still have to prove their clinical utility in improving the ability to characterize episodic memory capacity accurately.
1.4.1.2.2 Episodic and Semantic Memory in mTLE

Tulving’s early distinction between episodic and semantic memory rested on lesion data showing that patients with MTL damage had difficulties to recollect personal experienced events with a spatiotemporal context but had no difficulties to report conceptual knowledge about words, the world and the self (Tulving 1983; Tulving 2002). In current neuropsychological practice, this division is reflected in typical memory assessment, with emphasis on material specific laterality. For example, typical tests tapping episodic memory capacity are list learning of words or faces, such as the Warrington Words and Faces Recognition Test (Warrington 1984). In contrast, tests tapping semantic memory capacity are naming, vocabulary, and verbal fluency. Most standard neuropsychological tests that evaluate memory capacity adhere to this distinction and it is not surprising that patients with mTLE predominantly show a deficit in episodic and not semantic memory tasks (Warrington 1984; Morris, Abrahams et al. 1995). However, patients with TLE have been shown to be impaired at naming famous faces and providing semantic information about famous people (Viskontas, McAndrews et al. 2002). One explanation for these findings is that in addition to the MTL, LTCs were affected in these patients. Further, episodic and semantic memory systems might be supported by different critical brain regions but at least in the healthy brain they are in constant interaction with each other (Greenberg and Verfaellie 2010). For example, some patients with selective MTL damage have difficulties in a typical semantic category fluency task in which they are asked to retrieve as many members of a specific category within a short period of time as possible. However, it turns out that patients with MTL damage are only impaired if they use either an autobiographical or a navigational strategy to solve this task. Both of these strategies depend on intact MTLs to retrieve category members. Therefore, the use of different strategies can explain, at least in some circumstances, the impairment of patients with mTLE on semantic memory tasks (Greenberg, Keane et al. 2009).

1.4.1.2.3 Relational and Non-Relational Memory in mTLE

As reviewed above (see 1.3.1.2), MTL function can be even further fractionated in that the hippocampus has been shown to be crucially involved in relational processing and recollection which enable retrieval of contextually rich events while adjacent MTL structures, such as the perirhinal cortex can support item recognition via familiarity. As expected given the hippocampal involvement, patients with mTLE are impaired on relational memory tasks regardless of seizure or excision laterality (Moscovitch and McAndrews 2002; Cohn,
However, the literature regarding familiarity is mixed, sometimes showing intact (Moscovitch and McAndrews 2002) and sometime impaired (Cohn, McAndrews et al. 2009) item recognition abilities in mTLE. Most likely, this is due to perirhinal involvement in the disease process. Consistent with this idea, the patient N.B. who underwent a temporal lobe resection that spared the hippocampus showed impaired familiarity but intact recollection (Bowles, Crupi et al. 2007). From a clinical perspective, a number of authors have argued that a better appreciation of these aspects of memory fractionation (e.g., relational versus non-relational, pattern separation versus pattern completion) will be critical in moving forward in diagnosis and prognosis of mTLE (Saling 2009; McAndrews and Cohn 2012).

### 1.4.1.2.4 Autobiographical Memory in mTLE

There is a now good consensus in the patient literature that the MTLs are essential to retrieve vivid and detail-rich AMs. Whereas unilateral mTLE does not lead to a global autobiographical amnesia, there are marked deficits in the quality of AMs recalled (see Figure 1.4). Specifically, patients with mTLE are able to retrieve personal semantics, such as where they grew up and what school they attended but in general they have difficulties to recall personal episodic memories, such as a specific day during childhood (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009). Further careful explorations revealed that, whereas information about the story line or gist could be retrieved without problems, information about the visual-perceptual but also temporal and spatial details of AMs could not be retrieved easily (St-Laurent, Moscovitch et al. 2009). This lack of episodic details extends to the temporal domain, in that patients’ memory for the general temporal order of AMs tend to be intact, however, the memory for the minute-by-minute sequences tend to be impaired (St-Laurent, Moscovitch et al. 2011). In agreement with the proposal that AMs depend on the hippocampus as long as they can be retrieved, these impairments were found even in AMs from early childhood. Remarkably, these characteristics were equally present in patients pre- and postsurgically, with and without radiologically-confirmed MTS and with right or left mTLE (Viskontas, McAndrews et al. 2000). Interesting in this context, is that AMs have been shown to be dependent mostly on CA1 neurons (Bartsch, Dohring et al. 2011) and that these neurons are predominantly affected by sclerotic processes, even if not visible on MRI (Walker, Chan et al. 2007). It appears that even minimal damage to the hippocampus, maybe even specifically to the CA1 region, results in a significant impairment to recall personal autobiographical episodic
memories. This is unlike the graded deficits typically seen on other clinical tests of episodic memory in mTLE, in which the degree of impairment is correlated with the degree of MTL damage (Treynerry, Jack et al. 1993; Gleissner, Helmstaedter et al. 2002).

1.4.1.3 Predicting Memory Outcome

As noted above, in around a third of patients with mTLE, antiepileptic drugs do not result in a satisfactory seizure control and unilateral epilepsy surgery might be suggested to the patient. However, because the MTL is essential for episodic memory, surgical removal can result anywhere from an improvement to a severe decline of episodic memory function. In fact, postsurgical memory decline constitutes a major problem for patients after MTL resection. The next section will review the main attempts to predict postsurgical memory outcome in these patients.

1.4.1.3.1 Wada Test

In response to the concern about producing severe global amnesia after temporal lobe resection, Brenda Milner started to apply the Wada or intracarotid amobarbitol test which was already used to determine language laterality to the memory domain (Milner, Branch et al. 1962). The Wada test provides an opportunity to assess the functional status of both the ipsilateral and contralateral MTL during transient hemispheric anaesthesia. Presurgical Wada memory asymmetry has been found to be a reliable predictor of verbal memory outcome following left MTL resection and a less reliable predictor of visuospatial memory outcome following right MTL resection (Loring, Meador et al. 1995; Bell, Davies et al. 2000; Chiaravalloti and Glosser 2001). Importantly, the Wada test allowed for the first time not only to examine the integrity of ipsilateral MTL, but also whether the contralateral MTL could support memory function following surgery. This functional adequacy and reserve model was proposed as a new model to predict and understand the risk of postsurgical memory decline (Chelune 1995). In the meantime, the use of the invasive Wada test is now declining, as more recent studies suggest that its predictive value may be eclipsed by other sources of clinical information including neuropsychological testing and improving functional imaging technologies (Baxendale, Thompson et al. 2007; Elshorst, Pohlmann-Eden et al. 2009; Binder 2011).
1.4.1.3.2 Presurgical Memory Performance

Since the first experimental observations of memory changes pre- to postsurgically by Milner, it has been corroborated by a number of studies that patients displaying better presurgical material-specific memory performance show greater decline postsurgically, indicating the functional adequacy of the to-be-resected MTL (Helmstaedter and Kurthen 2001; Gleissner, Helmstaedter et al. 2002; Busch, Chapin et al. 2008; Helmstaedter, Richter et al. 2008). As will be apparent from the imaging literature, this pattern supports the idea that the structural and functional integrity of the epileptogenic MTL plays a key role in predicting memory outcome (Rausch 1987; Bonelli, Powell et al. 2010). Integrity in this sense is borrowed from electronics in which signal integrity means the system is in a state of being unimpaired, complete, and information can be transferred without corruption. In line with this proposal, the presence of structural abnormalities, such as MTS lessens the integrity of the MTL, therefore resulting in impaired presurgical memory performance and almost no change postsurgically (Rausch 1987; Trenerry, Jack et al. 1993). In this scenario, the patient is not at risk of declining much after surgery. On the other hand, resection of structurally and functionally intact tissue might lead to a bigger change pre- to postoperative. One drawback of behavioral measures of presurgical memory to predict postsurgical change is that these measures mainly try to assess functional adequacy and do not typically assess the reserve of the memory system.

1.4.1.3.3 Neuroimaging Predictors focusing on the MTL

Neuroimaging enables the clinician to examine the structural and functional integrity of the ipsilateral and contralateral MTL, therefore holding a great clinical promise. The interest in neuroimaging and mTLE is indicated by these several excellent reviews on this topic (Duncan 2009; Richardson 2010; McAndrews and Cohn 2012). Nonetheless, as will be discussed below, the findings are not as robust as expected.

To start with the most established piece, structural MTL abnormalities, such as MTS are a key feature of mTLE (Walker, Chan et al. 2007). Traditionally, structural imaging has therefore focused on volume and MR image intensity of MTL structures. Refined manual and automated segmentation techniques now allow a closer look at the structural changes typically seen in MTS (Pruessner, Li et al. 2000; Duchesne, Pruessner et al. 2002; Winterburn, Pruessner et al. 2013). In general, the anterior part of the MTL appears to be more severely impacted by sclerotic
processes than the posterior part. For example, the hippocampus head appears to be more atrophic than hippocampus body and tail and the entorhinal cortex is found to be more atrophied than the perirhinal cortex (Bernasconi, Bernasconi et al. 2003). Further, high-resolution MRI using a 4T MRI, revealed that hippocampal sclerosis predominantly affects CA subregions (Mueller, Laxer et al. 2009). In relation to episodic memory, the absence of MTS on MRI is associated with better presurgical memory performance and greater postsurgical decline (Trenerry, Jack et al. 1993; Elshorst, Pohlmann-Eden et al. 2009). This relationship is in line with the idea that the structural integrity of the ipsilateral hippocampus predicts the risk of postoperative memory change, thus reflecting the functional adequacy. However, despite the improvements in detecting structural MTL abnormalities with MRI, it is important to keep in mind that about half of the patients with mTLE do not show any MRI abnormalities (Walker, Chan et al. 2007), thus making the direct relationship between structural MRI abnormality and episodic memory capacity questionable.

On the other hand, functional MRI BOLD signal might provide a more accurate measure of MTL integrity as it allows examining whether and how much this tissue can be recruited by a specific task (see Figure 1.4). Broadly, memory fMRI studies in mTLE have shown reduced activity in the MTL on the side of seizure onset (Golby, Poldrack et al. 2002; Janszky, Joceit et al. 2005; Alessio, Pereira et al. 2013). For example, material-specific memory probes that are more likely to engage one or the other MTL in healthy controls (although see for a critical view (Kennepohl, Sziklas et al. 2007)) have been shown to activate the contralateral MTL in patients. That is, in patients with left mTLE, verbal memory tasks elicit greater activation in the right than left MTL (Golby, Poldrack et al. 2002), possibly pointing towards the functional reserve of the contralateral MTL or functional re-organization due to longstanding seizures. In agreement with this idea, the contralateral MTL showed increased metabolic activity (Trotta, Goldman et al. 2011) and could be recruited successfully to encode and retrieve episodic memories (Bonnici, Sidhu et al. 2013). Moreover, fMRI memory tasks that typically reveal bilateral MTL activation in healthy controls, such as scene encoding and AM retrieval, show reduced lateralized MTL activity in patients with mTLE (Detre, Maccotta et al. 1998; Jokeit, Okujava et al. 2001; Addis, Moscovitch et al. 2007). Together, these results suggest that memory-induced MTL activation might be a sensitive marker of functional adequacy. A reasonable expectation for the clinical neuropsychologist is that this measure of adequacy can be used to predict memory outcome. In
agreement with this proposal, there are now several studies showing that increased ipsilateral MTL activation is associated with greater decline postsurgically (Rabin, Narayan et al. 2004; Richardson, Strange et al. 2004; Powell, Richardson et al. 2008; Bonelli, Powell et al. 2010). However, there are also negative instances where MTL activation was sensitive to a particular task presurgically but did not predict memory outcome postsurgically (Binder, Swanson et al. 2010). Further, while two studies point to the potential role of examining the functional reserve with fMRI (Trotta, Goldman et al. 2011; Bonnici, Sidhu et al. 2013), this use of fMRI remains still relatively unexplored. Up to today, there is also little agreement on whether fMRI parameters provide independent or additional power to other indicators, such as neuropsychological tests and measures of MTS, to the prediction of memory outcome following surgery.

1.4.1.3.4 Multivariate Prediction

Most studies so far have focussed on the relationship between a single predictor and memory change postsurgically. Higher predictive values can be obtained by multivariable approaches that combine multiple, non-redundant sources of information. Generally, presurgical memory and structural MRI abnormalities seem to be the most reliable contributors to the prediction of memory outcome (Lineweaver, Morris et al. 2006; Baxendale, Thompson et al. 2007; Elshorst, Pohlmann-Eden et al. 2009; Binder 2011). Using a multivariate data reduction tool, principal component analysis, a recent study by our group aimed to reduce the number of individual neuropsychological test scores into composite verbal and visuospatial memory scores (St-Laurent, McCormick et al. 2013). These scores successfully classified patients according to their side of seizure origin and predicted postsurgically memory outcome. Another approach attempts to examine the relationship between structural and functional MTL integrity on episodic memory. Whereas generally both structural and functional integrity predict postsurgical memory outcome (Mechanic-Hamilton, Korczykowski et al. 2009), the relationship between structural abnormality and the level of BOLD signal becomes complicated by the fact that it follows most likely a nonlinear function (Sawrie, Martin et al. 2000; Dickerson, Salat et al. 2004). In fact, some patients with mTLE who demonstrate normal memory performance display greater activity in the both MTLs than controls and patients with mTLE who demonstrate impaired memory performance (Guedj, Bettus et al. 2011).
In sum, the traditional neuropsychological assessment of mTLE has, with good reason, focused on the MTL as the primary epileptogenic site and critical node for episodic memory. However, and as evident throughout this thesis, episodic memory does not rely solely on the MTL but engages a vast dynamically interacting network of brain regions to support this cognitive function. In addition, and as will become evident in the next section, mTLE is not a MTL-confined pathology. Rather, mTLE affects the intricate dialogue between hippocampus and neocortex in various instances and in turn affects the neuronal networks underlying episodic memory. This emerging knowledge about network changes in mTLE might significantly improve the prediction of postsurgical memory outcome.

1.4.2 Network Disruptions in Medial Temporal Lobe Epilepsy

1.4.2.1 Structural Network Disruptions in mTLE

As previously discussed, the hallmark lesion of mTLE is hippocampal sclerosis (Blumcke, Thom et al. 2002; Walker, Chan et al. 2007). However, histological reports of post-mortem brains demonstrate that pathology is not always limited to the hippocampus (Eriksson, Rydenhag et al. 2002; Blanc, Martinian et al. 2011). Indeed, in some cases, pathological cell loss and gliosis can be found in proximal and distal temporo-limbic regions, such as the amygdala, entorhinal cortex, LTC, and TempP. More recent autopsy reports have extended these observations by showing varying degrees of architectural abnormalities affecting virtually all lobes, if hippocampal sclerosis is present (Eriksson, Rydenhag et al. 2002; Blanc, Martinian et al. 2011). However, an impressive post-mortem study of H.M.’s brain revealed surprisingly normal histological architecture in the remaining MTL and brain tissue (Annese, Schenker-Ahmed et al. 2014). Nonetheless, these findings motivated the more in depth exploration of brain-wide structural network disruptions in patients with mTLE. As described previously, quantitative MRI analysis has offered the unique perspective to study these changes in vivo. In general, manual volumetric MRI analysis largely confirmed previous histological assessments, demonstrating volume loss in the ipsilateral hippocampus, entorhinal cortex, amygdala, TempP, perirhinal cortex, LTC, and thalamus (Bernasconi, Bernasconi et al. 2003; Sankar, Bernasconi et al. 2008). Automated segmentation techniques, such as VBM and cortical thickness analysis, on the other hand, have produced inconsistent findings which may be largely due to statistical power and applied thresholds (Keller and Roberts 2008; Pell, Briellmann et al. 2008; Li, Zhang et al. 2011; Eggert, Sommer et al. 2012). For example, in a relatively small study contrasting 12 patients to 19
healthy controls, patients showed extensive GMV loss throughout the brain, at a p < 0.001 uncorrected (Bouilleret, Semah et al. 2008). By comparison, a study contrasting 40 patients to 47 healthy controls, showed GMV loss only in the ipsilateral hippocampus and bilateral thalamus, at a p < 0.05, corrected for multiple comparisons (Bernasconi, Duchesne et al. 2004). Even further, contrasting 19 patients to 115 healthy controls, only the ipsilateral hippocampus showed reduced GMV in patients, again at p <0.05, corrected for multiple comparisons (Pell, Briellmann et al. 2008). In a highly informative meta-analysis of VBM studies in mTLE, the only consistent finding of GMV loss was found in the ipsilateral hippocampus (82% of all studies), followed by the PHC (47%), entorhinal cortex (23%), contralateral hippocampus (17%) and thalamus (ipsilateral 61% and contralateral 50%) (Keller and Roberts 2008). Using an alternative approach, cortical thickness analysis revealed wide-spread cortical thinning in patients with mTLE (Lin, Salamon et al. 2007); however, whether this method is as susceptible as VBM to produce false positive findings remains to be seen.

In addition to examining voxel-based structural changes, SCN can be studied through the covariance of MRI-based metrics such as VBM or cortical thickness (Bullmore, Woodruff et al. 1998; Evans 2013). In mTLE, several covariance analyses have mapped abnormal structural correlations between MTL and neocortical regions (Bonilha, Rorden et al. 2007; Bernhardt, Worsley et al. 2008). For example, correlating the thickness of the entorhinal cortex to that of the neocortex, patients with mTLE showed decreased structural coordination between MTL and LTCs, suggesting a connectional breakdown within temporo-limbic networks (Bernhardt, Worsley et al. 2008). Structural explorations using DTI, tapping into white matter connectivity, largely agree with voxel-based and SCNs in that patients with mTLE show decreased white matter integrity consistently within the temporo-limbic tracts, such as the fornix pathway, parahippocampal fibres, the uncinate fasciculus, and the cingulum bundle (Concha, Beaulieu et al. 2005; Gross, Concha et al. 2006; Concha, Beaulieu et al. 2007; Focke, Yogarajah et al. 2008; Concha, Beaulieu et al. 2009; Liu, Concha et al. 2012). These changes in white matter integrity, especially in the anterior and mesial temporal lobe seem to be related to memory performance (Riley, Franklin et al. 2010).

Whereas graph theoretical approaches yet have to prove their clinical value, it is interesting to notice that in mTLE, structural networks derived from both DTI and cortical thickness correlations are characterized by an increased clustering and path length, which are indicative of
a more regular global topology (Bernhardt, Chen et al. 2011; Bonilha, Nesland et al. 2012). These findings were complemented by the parallel observation of reduced network robustness, another measure of organizational stability (Bernhardt, Chen et al. 2011).

In sum, the most consistent finding of structural pathology in mTLE is decreased grey matter volume of the affected hippocampus and adjacent MTL structures, arguably extending to the LTC, TempP, and thalamus. The network findings presented here suggest further that volume loss within these regions is accompanied by a structural breakdown of the temporo-limbic network. On a brain-wide level, this reasonably localized damage might result in a more regular global network topology, which might in turn restrict the repertoire of functional connectivity patterns.

1.4.2.2 Functional Network Disruptions in mTLE

It is here where the three main themes of this literature review, networks of the brain, networks underlying episodic memory, and episodic memory networks affected by mTLE come together. As discussed previously, the traditional view on mTLE focused, with good reason, on the MTL as the primary site of damage and critical for episodic memory. However, we now know that the extensive repertoire of episodic memory, such as learning novel associations and the vivid mental reliving of an AM relies on a functional network that involves dynamic interactions between the MTL and other neocortical structures. In fact, network analysis revealed one of the most central brain networks the DMN significantly overlaps with the general co-activation partners of the MTL during AM retrieval and other recollection phenomena. What we know about how mTLE affects functional networks beyond the MTL and, especially, how networks underlying episodic memory are altered by mTLE are the last missing keystones to this literature review.

Given the structural damage seen in mTLE, functional network disturbances can be anticipated, and two reviews have recently summarized findings from resting state networks in mTLE (Bernhardt, Hong et al. 2013; Cataldi, Avoli et al. 2013). Most frequently, these networks are explored in a sample of unilateral mTLE ranging from 5-35 patients using ipsilateral MTL seeds and contrasting these seed-to-voxel connectivity matrices to those of healthy controls. The majority of these studies show that the affected MTL is no longer functionally connected to posterior regions of the brain, mainly the PCC and RSP (Waites, Briellmann et al. 2006; Zhang,
Lu et al. 2009; Morgan, Gore et al. 2010; Pereira, Alessio et al. 2010; Morgan, Rogers et al. 2011; Holmes, Folley et al. 2012; Pittau, Grova et al. 2012; Doucet, Osipowicz et al. 2013; Holmes, Yang et al. 2013; Ji, Zhang et al. 2013; Kucukboyaci, Kemmotsu et al. 2013; Maccotta, He et al. 2013; Trotta, Goldman et al. 2013; Haneef, Lenartowicz et al. 2014). However, to explore the full extent of functional network disturbances, seeding from the structurally disconnected MTL might not be the best strategy after all. For example, seeding from the contralateral hippocampus or other MTL structures revealed that in addition to reductions in functional connectivity, functional connectivity can also be increased (Bettus, Bartolomei et al. 2010; Maccotta, He et al. 2013; Trotta, Goldman et al. 2013; Haneef, Lenartowicz et al. 2014). In fact, Bettus et al. (2010) argued that increased functional connectivity of the contralateral basal temporal cortex might be a more reliable indicator of the primary epileptogenic zone than decreased functional connectivity within the ipsilateral basal temporal cortex. Other studies examining functional connectivity from the contralateral MTL to all other voxels of the brain revealed some increased long range connections but findings were inconsistent with respect to extent and localization, possibly due to varying degrees of pathological burden of the contralateral MTL (Maccotta, He et al. 2013; Trotta, Goldman et al. 2013; Haneef, Lenartowicz et al. 2014). Drawing on this idea, seeding from brain regions outside the MTL might reveal a more complete picture of functional network disturbances due to MTL damage. Indeed, functional connectivity from the PCC appears to be decreased to the affected MTL and other posterior brain regions (Waites, Briellmann et al. 2006; Haneef, Lenartowicz et al. 2012), whereas seeding from the anterior cingulate cortex appears to show increased connectivity to other frontal cortices, lateral temporal and lateral parietal cortices (Haneef, Lenartowicz et al. 2012). In line with these findings, a study examining functional connectivity between 90 cortical regions in bilateral mTLE revealed substantial decreases in functional connectivity throughout the cortex but also increased connectivity between frontal and lateral parietal cortices (Liao, Zhang et al. 2010). In sum, it appears that the MTL is disconnected from other regions of the brain, especially to the PCC, and that some connections, possibly between frontal and parietal areas are increased in mTLE in comparison to healthy controls.
1.4.2.3 Default Mode Network Disruptions in mTLE

In agreement with the findings outlined above, the most consistent finding of DMN alterations in mTLE is a reduction in functional connectivity between the affected MTL and the rest of the DMN (Voets, Adcock et al. 2009; Zhang, Lu et al. 2010; Liao, Zhang et al. 2011; Voets, Beckmann et al. 2012; James, Tripathi et al. 2013). Interestingly, it seems to be again the connection between the MTL and posterior part of the DMN that appears to be compromised. In fact, Voets et al. (2012) showed that the integration of the MTL into the posterior part of the DMN could be explained by GMV of the MTL whereas integration of the MTL into the middle and anterior part of the DMN seemed to be independent of MTL grey matter damage. These results might reflect the strong anatomical connection between the MTL and posterior regions of the DMN (see Figure 1.3). Indeed, this relationship is nicely illustrated by a recent study showing decreased white matter integrity between the hippocampus and RSP cortex and decreased functional connectivity along these connections (Liao, Zhang et al. 2011).

Figure 1.3: DMN Disruptions in Patients with mTLE

Panel A displays example of DTI tractography on one control and one patient with bilateral mTLE. Three fibre bunches located between the PCC/RSP, medial prefrontal cortex and bilateral MTLs are displayed. Color-coding indicates the direction of the fibres. Green indicates dorsoventral and blue indicates rostro-caudal direction. Panel B displays functional connectivity between the PCC/RSP, medial prefrontal cortex and bilateral MTLs in controls and patients with bilateral mTLE. This figure is reproduced with permission from (Liao, Zhang et al. 2011).
Nonetheless, little is known about how these functional disturbances map onto the specific episodic memory impairment in these patients and this question is a central topic of this thesis. A recent study examining the relationship between connectivity from the affected hippocampus and episodic memory in 11 patients with left mTLE found that connectivity between PCC and affected hippocampus (PCC-HC) was among the few regions that correlated positively with episodic memory (Holmes, Folley et al. 2012). In contrast, another study, seeding only from the most atrophic, anterior portion of the hippocampus revealed a negative correlation between PCC-HC connectivity and episodic memory (Doucet, Osipowicz et al. 2013). This discrepancy between these studies might reflect either the potential different functional roles of the posterior and anterior segments of the hippocampus, or that seeding from the most affected portion of the hippocampus is most sensitive in revealing a dysfunctional relationship to the PCC.

1.4.2.4 Memory Network Disruptions in mTLE

Whereas recent advances have explored structural and functional network changes in mTLE, far less is known about how mTLE impacts flexible networks supporting episodic memory (see Figure 1.4). As discussed above, several lines of evidence suggest the hippocampus as a critical hub to form transient neocortical networks (see 1.3.2). Further, it has been suggested that a measure of the capability to accomplish this coordinating role might be signal complexity or variability that allows the system to explore various functional states. In agreement with this proposal, iEEG signals recorded from the epileptogenic hippocampus in patients with mTLE show less complexity compared to the contralateral, non-epileptic hippocampus (Protzner, Valiante et al. 2010). This idea was further corroborated in a recent fMRI study illustrating that variability of BOLD signal in the affected hippocampus across a variety of cognitive tasks could predict clinical memory performance (Protzner, Kovacevic et al. 2013). This line of evidence suggests that damage to the hippocampus leads to a compromised capability to flexibly alternate between different process specific alliances or react to different neuronal contexts.

On a brain wide level, a seminal study revealed that effective connectivity was altered throughout a network supporting AM in patients with mTLE (Addis, Moscovitch et al. 2007). Interestingly, whereas in healthy controls the left hippocampus was strongly integrated in this network, in patients with left mTLE, these connections were decreased and long-range
connections from RSP cortex to amPFC were increased. Consistent with this pattern, another study revealed that strong connectivity between hippocampus and PFC during a verbal associative task was associated with presurgical better verbal learning but greater memory deterioration postsurgically (Wagner, Frings et al. 2007). These findings suggest that the integration of the hippocampus within a functional network can be used as an indicator of episodic memory capacity. Further, this disturbed integration might lead to compensatory strengthening of other routes in the attempt to complete the task at hand. Indeed, patients with mTLE have been shown to rely on a different episodic memory encoding network than healthy controls (Sidhu, Stretton et al. 2013). Alternatively, although not mapping memory explicitly, another study from our lab revealed that patients with mTLE revealed a similar language network as healthy controls, but a different pattern of connectivity explained performance on a clinical test in controls and patients (Protzner and McAndrews 2011). Together, these studies demonstrate that functional neuronal networks underlying episodic memory capacity are altered in mTLE.
Figure 1.4: AM Retrieval and Functional Network Disruptions in Patients with mTLE

Panel A summarizes AM retrieval deficits in patients with unilateral mTLE. Patients have difficulties to retrieve internal event-specific details, such as temporal (Ti), perceptual (pe) and thought-related details (Th). These patients have no deficits in remembering the general story events (Ev), place details (Pl) or any of the measures of external details, such as semantic (Sem) information or repetitions (Repet) and other AM elements. **p<0.01, ***p<0.001. Reproduced with permission from (St-Laurent, Moscovitch et al. 2009).

Panel B displays hippocampal activation during AM retrieval in healthy controls (left), patients with left TLE (middle) and the contrast between controls and patients (right).

Panel C illustrates effective connectivity changes between controls and patients with left TLE during AM retrieval. Significant connections are displayed in color. Red indicates a positive influence and blue indicates a negative influence on the target node. Arrow thickness represents the strength of the connection. Connections that did not differ between groups are depicted in black. Note that controls rely on a hippocampal-centric network while patients with left TLE rely on long range connections between the medial parietal (MPC) and medial prefrontal cortex.
(MPFC). L=Left, R= Right, HC=Hippocampus, tPOLE=Temporal pole, PHG=Parahippocampal gyrus, TPJ=Temporoparietal junction. Panel B and C are reproduced with permission from (Addis, Moscovitch et al. 2007).
Panel D displays differences in multiscale entropy estimated in the epileptogenic right (RHC) and non-epileptogenic left (LHC) hippocampus in patients with right mTLE. Left graph shows group mean entropy with standard errors. Stars indicate temporal scales at which the PLS contrast shown in the right graph is stably expressed. Reproduced with permission from (Protzner, Valiante et al. 2010).

1.4.3 Summary

mTLE is characterized by recurrent seizures originating from the MTL. A third of patients with mTLE continue to have seizures despite antiepileptic treatment and in unilateral cases, surgical MTL resection might be an option to obtain seizure freedom. However, removal of the MTL which is critical for episodic memory results in some cases in drastic declines in memory function. Therefore, much effort has been spent to evaluate the functional adequacy and reserve of the MTLs to predict postsurgical memory outcome.

However, recent advances in neuroimaging have challenged the idea of mTLE being only a MTL pathology. Evidence from structural network analysis suggests that at least the LTC and TempP are also affected, in that they show reduced GMV and cortical thickness. Functional connectivity alterations in patients with mTLE are even further distributed. The most common functional disruption appears to be the connection between the affected MTL and posterior part of the DMN which also seems to be related to clinical memory performance. In addition, a growing number of studies reveal increases in functional connectivity which might point towards compensatory or functional reserve mechanisms. Indeed, the few studies comparing memory networks in patients with mTLE to healthy controls illustrate either wide-spread alterations in patients or the use of a different network structure altogether. Despite the tremendous advances in exploring networks related to mTLE, several important topics remain relatively unexplored. For example, little is known about whether these resting state network changes relate to episodic memory capacity, whether these measures could be used in a clinical setting, and how mTLE damage influences the capacity to engage subnetworks flexibly during episodic memory retrieval. Those are the foci of the current experiments.
2  Research Aims and Hypotheses
2.1 DMN Connectivity and Episodic Memory Capacity in Patients with mTLE

Historically, studies examining episodic memory function in patients with mTLE have focused mainly on the affected hippocampus and adjacent MTL cortices. These studies revealed that typically higher indices of healthy hippocampal tissue (e.g., absence of MTS) are associated with better episodic memory capacity (Trenerry, Jack et al. 1993; Bell, Lin et al. 2011). Further, if the MTL is surgically removed to treat medically intractable mTLE, indicators of better pre-surgical integrity of hippocampal tissue are associated with greater decline in episodic memory capacity postsurgically (Trenerry, Jack et al. 1993; Elshorst, Pohlmann-Eden et al. 2009). A major drawback of these predictors however is their relatively low individual predictive value. One contributing factor to poor prediction might be that they neglect the network perspective. That is, functional connectivity studies suggest that episodic memory is supported by brain wide networks, integrating hippocampi and neocortical regions into configurations of transient connectivity (Dickerson and Eichenbaum 2010; Rugg and Vilberg 2013). For example, during AM retrieval and the subjective feeling of recollection, hippocampal activation is most often accompanied by activation in other brain regions, such as the PCC/RSP, amPFC, lateral parietal cortex and LTC (Addis, McIntosh et al. 2004; Spreng, Mar et al. 2009; Spreng and Grady 2010; Rugg and Vilberg 2013).

Interestingly, these regions are also constituents of the DMN which has been suggested as one of the core resting state networks of the brain (Buckner, Andrews-Hanna et al. 2008; Hagmann, Cammoun et al. 2008). Together, these regions are strongly structurally and functionally connected (Honey, Sporns et al. 2009) even during rest, anesthesia (Vincent, Patel et al. 2007) and early stages of sleep (Fukunaga, Horovitz et al. 2006). Further, computational simulations predict that focal lesions to DMN nodes cause widespread disruptions of functional connectivity within and beyond the DMN (Alstott, Breakspear et al. 2009). While empirical lesion data show disrupted DMN connectivity in patients with various neurological and psychiatric disorders (Zhang and Raichle 2010), little is known about how these alterations map onto specific cognitive deficits.
From that perspective, patients with mTLE offer the opportunity to study the effects of reasonable focal damage to the DMN as epileptic seizures arise only from the MTL and a selective neuropsychological impairment on episodic memory tasks. These observations led to the first main goal of the current thesis, to explore how MTL damage affects DMN connectivity and how these changes relate to episodic memory function.

2.1.1 Specific Hypotheses for the First Study

In the first study of this thesis, we focused on the functional connection between the hippocampus and the main hub of the DMN, the PCC (PCC-HC), and evaluated its association with presurgical episodic memory capacity, and its ability to indicate postsurgical memory changes. The PCC as primary seed was chosen because this region is not typically affected in mTLE (Keller and Roberts 2008) and is one of the few regions that has been found to be activated in both recognition and relational memory paradigms (McDermott, Szpunar et al. 2009). We addressed the following hypotheses:

1. Connectivity between the PCC and affected hippocampus is reduced in patients with mTLE in comparison to healthy controls.
2. Stronger connectivity between the PCC and affected hippocampus is associated with better episodic memory capacity.
3. Stronger connectivity between the PCC and affected hippocampus is associated with greater decline in episodic memory capacity postsurgically.

2.1.2 Specific Hypotheses for the Second Study

In the second study, we examined whether unilateral structural damage to the MTL would cause widespread functional DMN connectivity alterations that have been predicted by computational models. We further aimed to extend the results of the first study by investigating whether patterns of DMN connectivity, rather than just PCC-HC connectivity would be associated with episodic memory capacity. Here are the specific hypotheses for the second study:

1. Focal structural damage to the MTL causes widespread DMN connectivity alterations.
2. Those alterations follow specific patterns that can be characterized by decreased interhemispheric connectivity and increased intrahemispheric connectivity.
3. These patterns of DMN disruptions reflect patient-specific episodic memory capacity.
2.2 Flexible hippocampal-neocortical interactions during AM retrieval

Several ideas emerged about the flexible interplay between the hippocampus and other brain regions to support very specific instances of episodic memory processes. For example, the model of the neuronal context proposes that a function of a brain region is dependent on the current state of the entire network (McIntosh 1999). The process-specific alliances are derived from a similar model, suggesting that brain regions are bound together transiently to perform a specific task (Moscovitch 1992; Cabeza and Moscovitch 2013). Importantly, these process specific alliances might also extend beyond DMN regions. The second set of studies of this thesis focused on the flexible hippocampal-neocortical interactions during active episodic, AM retrieval. AM retrieval can be seen as a special case of cued recall of contextually rich episodic memories. This complex cognitive process has been shown to consist of two different stages, the construction stage in which a specific AM is retrieved and an elaboration stage in which episodic details are retrieved from this specific life event (Addis, Wong et al. 2007). This dissociation allowed us to examine whether hippocampal-neocortical interactions differ between these AM retrieval stages. We formulated our hypotheses further based on an influential model developed by Conway (Conway and Pleydell-Pearce 2000; Conway 2009) about the organization of AM. Based on EEG and positron emission tomography (PET) findings, Conway (Conway, Turk et al. 1999; Conway, Pleydell-Pearce et al. 2001) argued that fronto-temporal cortices might be important for AM construction, whereas AM elaboration would be supported by a widespread posterior, perceptual network, including occipital, parietal and temporal cortices. Other studies examining the neural correlates of AM construction and elaboration revealed sustained hippocampal activation (Addis, Wong et al. 2007; St Jacques, Kragel et al. 2011). We therefore extended Conway’s model (Conway and Pleydell-Pearce 2000; Conway 2009) by hypothesizing that the hippocampus would be the main hub coordinating this neocortical dialogue and that damage to the hippocampus would significantly impair this interplay.
2.2.1 Specific Hypotheses for the Third Study

In the third study, we focused on the flexible hippocampal-neocortical dialogue during AM construction and elaboration in healthy controls. We used functional and effective connectivity analyses to examine whether the hippocampus coordinates these transient network constellations. The specific hypotheses of the third study are as follows:

1. During AM construction, the hippocampus is connected to a fronto-temporal network.

2. During elaboration, the hippocampus is connected to a widespread occipito-parieto-temporal network.

2.2.2 Specific Hypotheses for the Fourth Study

The fourth study builds upon the results of the third study. Here, the goal was to examine how MTL damage affects the flexible hippocampal-neocortical interplay during AM construction and elaboration. As described in the literature review, patients with mTLE have been shown to have an impairment in recalling vivid episodic elements of specific AMs (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011). Further, hippocampal signal variability is reduced in the damaged in comparison to the contralateral hippocampus (Protzner, Valiante et al. 2010). Together, these findings suggest that patients with mTLE do not engage the hippocampal-neocortical interactions in the same way as healthy controls do. Thus, we hypothesized that the ability to support these flexible network changes is reduced in patients with mTLE. Here are the specific hypotheses for study four:

1. Patients with mTLE show reduced hippocampal activation during AM retrieval in comparison to healthy controls.

2. In comparison to healthy controls, patients with mTLE show reduced hippocampal-neocortical connectivity fluctuations between AM construction and elaboration.
3 Default Mode Network Connectivity indicates Episodic Memory Capacity in Medial Temporal Lobe Epilepsy

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3.1 Abstract

Purpose: The clinical relevance of resting state functional connectivity in neurological disorders, including mesial temporal lobe epilepsy (mTLE), remains unclear. This study investigated how connectivity in the default mode network changes with unilateral damage to one of its nodes, the hippocampus (HC), and how such connectivity can be exploited clinically to characterize memory deficits and indicate postsurgical memory change.

Methods: FMRI resting state scans and neuropsychological memory assessments (Warrington Recognition Tests for Words and Faces) were performed on 19 healthy controls, 20 right and 18 left mTLE patients. In addition, postsurgical fMRI resting state and memory change (postsurgical memory performance – presurgical memory performance) data were available for half of these patients.

Key findings: Patients with mTLE showed reduced connectivity from the posterior cingulate cortex (PCC) to the epileptogenic HC and increased PCC connectivity to the contralateral HC. Stronger PCC connectivity to the epileptogenic HC was associated with better presurgical memory and with greater postsurgical memory decline. Stronger PCC connectivity to the contralateral HC was associated with less postsurgical memory decline. Following surgery, PCC connectivity to the remaining HC increased from presurgical values and showed enhanced correlation with postsurgical memory function. Importantly, this index was superior to others (hippocampal volume, pre-operative memory scores) in explaining variance in memory change following surgery.

Significance: Our results demonstrate the striking clinical significance of the brain’s intrinsic connectivity in evaluating cognitive capacity and indicating the potential of postsurgical cognitive morbidity in mTLE patients.
3.2 Introduction

FMRI resting state connectivity allows the examination of neuronal networks based on intrinsic BOLD fluctuations that exhibit a high degree of synchrony between structurally and functionally related brain regions (Fox and Raichle 2007; Honey, Sporns et al. 2009). Whereas this technique has shown considerable utility describing network differences between patients with neuropsychiatric or neurological diseases and healthy participants (Zhang and Raichle 2010; Khamsi 2012), determining whether these changes in connectivity reflect the specific cognitive deficits in these disorders or can predict changes in brain function following intervention remain open questions.

These questions have major clinical implications for patients with drug-resistant unilateral mesial temporal lobe epilepsy (mTLE) who are considered candidates for epilepsy surgery. Unilateral mTLE is characterized by recurrent seizures originating in the hippocampus (HC) and related mesial temporal lobe (MTL) structures which are known to be crucial in supporting episodic memory (Milner 1958; Ranganath 2010). Therefore, patients with mTLE have deficits in a variety of episodic memory tasks, including hemisphere-specific verbal and non-verbal learning and retrieval, associative retrieval and vivid autobiographical recall (McAndrews and Cohn 2012). Even further decline in episodic memory performance often results from surgical removal of the epileptogenic MTL (Sherman, Wiebe et al. 2011). Therefore, the ability to accurately evaluate presurgical episodic memory capacity and predict changes postsurgically is crucial for clinicians and patients in order to make informed decisions regarding epilepsy surgery.

A major drawback of standard predictors of postsurgical memory decline, such as neuropsychological memory test batteries (Baxendale, Thompson et al. 2006; Helmstaedter, Richter et al. 2008), measures of structural MTL damage (Helmstaedter and Kurthen 2001), as well as newer techniques such as task-related fMRI activation in the HC (Bonelli, Powell et al. 2010), is their rather low individual predictive value, which is notably better in multivariable models (Baxendale, Thompson et al. 2006; Bonelli, Powell et al. 2010). One factor contributing to poor prediction is that most models focus primarily on the functional adequacy of the damaged MTL, thereby neglecting more widespread network disruptions commonly found in mTLE (Addis, Moscovitch et al. 2007; Bell, Lin et al. 2011). In contrast, the evaluation of
functional connectivity among brain structures that support episodic memory widens this focus to a more comprehensive perspective that also speaks to the functional reserve of brain networks for supporting memory postsurgically and may significantly improve the prediction of postsurgical memory decline.

Interestingly, one of the most robust and well-studied resting state networks, the default mode network (DMN) (Buckner, Andrews-Hanna et al. 2008), consists of brain regions also commonly activated by episodic or autobiographical memory retrieval tasks (Svoboda, McKinnon et al. 2006; Spreng and Grady 2010). This substantial overlap suggests that the degree of connectivity within the DMN may be used as an indicator of episodic memory capacity that can be exploited clinically, especially in patients with memory impairments.

The fact that epileptic seizures in patients with unilateral mTLE arise from only one region of the DMN, coupled with selective impairments within the episodic memory domain, suggests that this clinical population offers the unique opportunity to study the effects of focal DMN disruptions and surgical intervention on episodic memory capacity. Whereas previous fMRI studies have shown that the epileptogenic MTL is disconnected from the rest of the DMN (Zhang, Lu et al. 2010; Liao, Zhang et al. 2011; Pittau, Grova et al. 2012), to our knowledge no study has yet related these disruptions to behaviour or has explored potential compensatory changes. In this study, we therefore evaluate strength of connectivity of the ‘hub’ of the DMN (posterior cingulate cortex, PCC) and the hippocampus, its association with presurgical episodic memory capacity, and its ability to indicate postsurgical memory changes.

### 3.3 Methods

#### 3.3.1 Participants

We included 57 participants in this study: 20 patients with right mTLE, 18 with left mTLE and 19 healthy participants. A subgroup of these patients (9 left mTLE, 10 right mTLE) underwent epilepsy surgery and were evaluated both pre- and post-operatively. All participants gave written consent to this study which was approved by the UHN Research Ethics Board. Each patient had
the diagnosis of unilateral mTLE based upon localization of seizure focus to the MTL during extended EEG and video monitoring. Presence of mesial temporal lobe sclerosis (MTS) was determined by a neuroradiologist at our epilepsy clinic (see Table 3.1 for demographic and clinical information). All patients that underwent epilepsy surgery were seizure-free at the time of postsurgical testing.

3.3.2 MRI Acquisition and Preprocessing

We analyzed six minutes of resting state fMRI for each participant. The same protocol was used at post-operative scanning that occurred at least six months after surgery. The first three frames of each session were dropped to allow signal equilibrium. Participants were asked to close their eyes and relax during scanning. All MRI data were acquired on a 3T Signa MR System (GE MedicalSystems, Milwaukee WI). The anatomical scans consist of a T1-weighted sequence, 146 slices, 220mm FOV, 1mm slice thickness, voxelsize 0.86x0.86x1mm, 0 gap. T2*-weighted functional data were acquired in an interleaved order, between 28 and 32 slices to cover the whole brain, 240mm FOV, 5mm slice thickness, voxelsize 3.75x3.75x5mm, 0 gap, TE=30msec, TR=2sec. fMRI data were taken in an oblique orientation, with each slice being perpendicular to the long axis of the hippocampus. Patient and control MRI data were acquired between 2007 and 2011. All fMRI data were preprocessed using the software package SPM8 (Statistical Parametric Mapping 8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Functional data were realigned and unwarped, and spatially normalized to the MNI EPI template. 2 controls, 3 patients with left and 3 patients with right mTLE had head motion parameters that exceeded 1.5mm but not 2.5mm in any direction at any given time. Further, voxel size was resampled to 3x3x3mm and smoothed with a full width half maximum (FWHM) of the Gaussian smoothing kernel of 8x8x8mm. The data were temporally bandpass filtered (0.01 to 0.1 Hz) and corrected for head motion (i.e., six head motion regressors from SPM realignment procedure), white matter and ventricular signal using the conn toolbox (http://www.nitrc.org/projects/conn). Visual inspection confirmed that the normalized remaining HC and PCC of the postsurgical scans overlaid with the MNI EPI image. Although the effect of interictal epileptic discharges on the BOLD effect is not clear (Laufs, Hamandi et al. 2007; Gotman and Pittau 2011), we did examine each participants’ raw data using ART (artifact detection tools, http://www.nitrc.org/projects/artifact_detect) to check for outliers in BOLD signal intensities and found no obvious ‘spikes’ and no differences between controls and patients.
Table 3.1: Demographical and Clinical Information (Study 1)

<table>
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<tr>
<th></th>
<th>Left mTLE (n=18)</th>
<th>Right mTLE (n=20)</th>
<th>Controls (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>(n=18)</td>
<td>(n=20)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
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<td>9/11</td>
<td>9/10</td>
<td></td>
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<tr>
<td>Handedness (right/left)</td>
<td>16/2</td>
<td>16/4</td>
<td>17/2</td>
<td></td>
</tr>
<tr>
<td>Age at scan, mean (SD)</td>
<td>36.2 (12.4)</td>
<td>37.3 (11.8)</td>
<td>(9.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
<td>14.6 (2.9)</td>
<td>13.2 (2.8)</td>
<td>(3.4)</td>
<td>*c</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS (yes/no)</td>
<td>13/5</td>
<td>13/7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Left HC volume</td>
<td>2.6 (0.6)</td>
<td>2.9 (0.3)</td>
<td>3.1 (0.4)</td>
<td>***c</td>
</tr>
<tr>
<td>Right HC volume</td>
<td>2.8 (0.2)</td>
<td>2.5 (0.5)</td>
<td>3.0 (0.4)</td>
<td>**c</td>
</tr>
<tr>
<td>Age of onset, mean (SD)</td>
<td>15.8 (13.0)</td>
<td>19.3 (14.8)</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Epilepsy duration</td>
<td>20.6 (14.9)</td>
<td>17.9 (13.3)</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Language lateralization (L/R)</td>
<td>17/0</td>
<td>17/1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presurgical group size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>presurgical WWR, mean (SD)</td>
<td>44.5 (4.0)</td>
<td>46.8 (2.5)</td>
<td>(1.0)</td>
<td>*d</td>
</tr>
<tr>
<td>presurgical WFR, mean (SD)</td>
<td>40.5 (5.9)</td>
<td>39.4 (5.7)</td>
<td>(3.1)</td>
<td>*d</td>
</tr>
<tr>
<td>Postsurgical group size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between memory evaluations, months (SD)</td>
<td>24.0 (7.2)</td>
<td>21.2 (5.2)</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time between surgery and memory evaluation, months (SD)</td>
<td>9.1 (3.7)</td>
<td>8.6 (3.5)</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time between surgery and second imaging, months (SD)</td>
<td>7.4 (2.4)</td>
<td>6.9 (1.3)</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>postsurgical WWR, mean (SD)</td>
<td>40.4 (5.4)</td>
<td>48.2 (1.5)</td>
<td>-</td>
<td>*e</td>
</tr>
<tr>
<td>WWR change, mean (SD)</td>
<td>-2.5 (5.3)</td>
<td>1.3 (1.7)</td>
<td>-</td>
<td>*e</td>
</tr>
<tr>
<td>postsurgical WFR, mean (SD)</td>
<td>40.4 (5.3)</td>
<td>35.1 (5.6)</td>
<td>-</td>
<td>*e</td>
</tr>
<tr>
<td>WFR change, mean (SD)</td>
<td>1.9 (3.3)</td>
<td>-3.4 (3.9)</td>
<td>-</td>
<td>*e</td>
</tr>
</tbody>
</table>

SD = standard deviation, MTS = mesial temporal lobe sclerosis, WWR = Warrington Words Recognition, WFR = Warrington Face Recognition, change = postsurgical minus presurgical WWR/WFR performance

*a* All patients had clinically confirmed hippocampal seizure onset, irrespective of whether they had MTS.

*b* Mean volumes are reported in mm3 adjusted by the intracranial volume and multiplied by 1000

*c* ANOVA between all three groups

*d* Unpaired, two-tailed T-Test for 1. WWR between controls and left mTLE, and 2. WFR between controls and right mTLE

*e* Unpaired, two-tailed T-Test between left mTLE and right mTLE

*f* Language lateralization based on fMRI (language lateralization of 3 patients were not available)

*p*<0.05, **p*<0.1, ***p*<0.001
3.3.3 Data Analysis

3.3.3.1 Structural Evaluation of Hippocampal Volume

We used the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/) to extract HC volume in both hemispheres in patients with mTLE. The automated procedure for volumetric measures is described in detail elsewhere (Fischl, Salat et al. 2002) and has been successfully applied to patients with mTLE (McDonald, Hagler et al. 2008). In brief, anatomical MRI scans were registered to the Talairach atlas using high-dimensional nonlinear volumetric alignment parameters. The final volumetric segmentation and labeling in this automated pipeline are based on both a subject-independent probabilistic atlas and subject-specific measured values. All segmentations were visually inspected prior to inclusion in the group analysis and no segmentation errors were identified. As reported below, our patient cohort showed the expected reduction in HC volume in the epileptogenic but not contralateral hemisphere (see Table 3.1).

3.3.3.2 Regions of Interest

We included 19 ROIs (8mm spheres) based on coordinates specified in a recent comprehensive analysis of the DMN (Andrews-Hanna, Reidler et al. 2010) (see Table 3.2 for all ROIs and MNI coordinates). For midline regions (PCC and medial prefrontal cortex), time series were averaged across left and right ROIs; all others were treated separately by hemisphere.

3.3.3.3 Functional Connectivity Analysis

Our selection of the PCC as the primary seed for these analyses was based on these considerations: (1) it is considered the primary ‘hub’ of the DMN (Fransson and Marrelec 2008; Hagmann, Cammoun et al. 2008), (2) it is not known to be primarily affected in mTLE (Bernhardt, Bernasconi et al. 2010; Li, Zhang et al. 2011), and (3) it is one of very few regions that has been found to be activated in both recognition and relational retrieval memory paradigms (McDermott, Szpunar et al. 2009).

Timeseries of voxels within each ROI were averaged and correlated with the averaged timeseries of the other ROIs. Correlation values were then z-transformed to the mean of the whole sample. Then, the average correlation matrix for each group was calculated and thresholded at p<0.05 false discovery rate (FDR). Second-level random effects analyses were conducted contrasting patients and healthy participants. Because the hippocampal ROI defined in the a priori set
included only anterior hippocampus, we applied an anatomically-defined mask of the whole HC (Marina, http://bion.de) which matched MNI normalized fMRI data to the PCC-to-voxel correlation maps (p<0.05 svc (small volume corrected), cluster size of > 10 voxels). In order to compare pre- and postsurgical PCC-HC connectivity for patients with left and right mTLE, we performed paired t-tests for each group separately, thresholded for positive values only, p<0.05 svc, cluster size > 10 voxels.

Table 3.2: DMN Regions of Interest and MNI Coordinates

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>Abbreviation</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal formation</td>
<td>left</td>
<td>lHC</td>
<td>-22</td>
<td>-20</td>
<td>-26</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rHC</td>
<td>22</td>
<td>-20</td>
<td>-26</td>
</tr>
<tr>
<td>Parahippocampal cortex</td>
<td>left</td>
<td>lPHC</td>
<td>-28</td>
<td>-40</td>
<td>-12</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rPHC</td>
<td>28</td>
<td>-40</td>
<td>-12</td>
</tr>
<tr>
<td>Retrosplenial cortex</td>
<td>left</td>
<td>lRsp</td>
<td>-14</td>
<td>-52</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rRsp</td>
<td>14</td>
<td>-52</td>
<td>8</td>
</tr>
<tr>
<td>Posterior inferior parietal lobule</td>
<td>left</td>
<td>lIPL</td>
<td>-44</td>
<td>-74</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rIPL</td>
<td>44</td>
<td>-74</td>
<td>32</td>
</tr>
<tr>
<td>Ventral medial prefrontal cortex</td>
<td>midline</td>
<td>vmPFC</td>
<td>0</td>
<td>26</td>
<td>-18</td>
</tr>
<tr>
<td>Dorsal medial prefrontal cortex</td>
<td>midline</td>
<td>dmPFC</td>
<td>0</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>left</td>
<td>lTempP</td>
<td>-50</td>
<td>14</td>
<td>-40</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rTempP</td>
<td>50</td>
<td>14</td>
<td>-40</td>
</tr>
<tr>
<td>Lateral temporal cortex</td>
<td>left</td>
<td>lLTC</td>
<td>-60</td>
<td>-24</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rLTC</td>
<td>60</td>
<td>-24</td>
<td>-18</td>
</tr>
<tr>
<td>Temporal parietal junction</td>
<td>left</td>
<td>lTPJ</td>
<td>-54</td>
<td>-54</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rTPJ</td>
<td>54</td>
<td>-54</td>
<td>28</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>left</td>
<td>lPCC</td>
<td>-8</td>
<td>-56</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>rPCC</td>
<td>8</td>
<td>-56</td>
<td>26</td>
</tr>
<tr>
<td>Anterior medial prefrontal cortex</td>
<td>left</td>
<td>lamPFC</td>
<td>-6</td>
<td>52</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>ramPFC</td>
<td>6</td>
<td>52</td>
<td>-2</td>
</tr>
</tbody>
</table>

Coordinates are based on MNI system and represent the center of 8mm spheres. Left hemispheric coordinates are taken from (Andrews-Hanna, Reidler et al. 2010).
3.3.3.4 Graph Analytic Analysis

For this analysis, we separated left and right PCC ROIs resulting in 20x20 correlation matrices. Using Sporn’s brain connectivity toolbox (BCT, https://sites.google.com/a/brain-connectivity-toolbox.net/bct/), we applied a proportional threshold on the individual correlation matrices so that only the strongest 50% of correlation values survived and binarized the resulting matrix. This procedure ensures that patients and controls have the same amount of connections in the graph, therefore avoiding group biases. As this threshold is somewhat arbitrary, we compared results with different thresholds (see Figure 3.1). Then, the degree (i.e., the number of connections that link one ROI to the rest of the network) was calculated for each ROI in each participant. Differences in degree for HC ROIs within the same group were assessed using one-tailed paired t-tests, whereas differences in degree for all other ROIs between the three groups were assessed using ANOVAs with a significance threshold of p<0.05 (see Figure 3.3 for degree distribution and Figure 3.4 for group differences in DMN subsystems).

Figure 3.1: Hippocampal Degree as a Function of Threshold

These graphs show degrees of the right (rHC) and left HC (lHC) for controls (left), patients with left mTLE (middle) and right mTLE (right) as a function of proportional threshold. For example, at a proportional threshold of 3.0, only the strongest 30% of correlation values were set to one, thus defining the number of connections in the binary connectivity matrix. At a threshold of 6.0, the strongest 60% of correlation matrix were included in the connectivity matrix. *

= because of our apriori hypothesis that the damaged HC should have a smaller degree than the contralateral HC, we applied a significance threshold of p<0.05 one-tailed, paired t-test.

3.3.4 Episodic Memory Measures

We selected two episodic memory tests that have demonstrated good clinical sensitivity and specificity for detecting unilateral memory impairments in our clinical practice with mTLE patients (Morris, Abrahams et al. 1995; Cohn, McAndrews et al. 2009): the Warrington Words
Recognition Test (WWR) as a measure of verbal memory typically associated with left MTL integrity and the Warrington Faces Recognition Test (WFR) as a measure of non-verbal memory which is mainly supported by the right MTL. Patients that had undergone epilepsy surgery received, between 6 and 12 months after surgery, postsurgical memory evaluation. Based on these memory scores we calculated memory change following surgery by subtracting presurgical from postsurgical memory scores. As we report below, our patient cohort also showed the expected material-specific memory impairment and postsurgical decline (see Table 3.1).

3.3.5 Correlations between PCC-HC Connectivity and Episodic Memory Measures

For each group, a voxelwise one-sample t-test was conducted with one behavioural measure (e.g., presurgical verbal memory performance) as a covariate of interest. Again, HC masks were applied and results were thresholded at p<0.05, svc, cluster size > 10 voxels. Of note, as we had directional hypotheses, we only report positive correlations for the pre- and postsurgical brain-behaviour relationships; however, we considered positive and negative correlations in order to assess functional adequacy and reserve of postsurgical memory change. To visualize the actual correlation between PCC-HC connectivity and memory measures, peak connectivity values were extracted using SPM8 and correlated with memory measures, i.e., no secondary statistics were performed.

3.3.6 Comparison between Predictors

We evaluated whether PCC-HC\(^1\) connectivity indicates postsurgical memory decline more accurately than two standard predictors, presurgical memory performance and structural volume loss in the hippocampus. For the presurgical memory performance, we correlated the presurgical performance of the WWR (in left mTLE) and WFR (in right mTLE) with memory change scores for these tests. As a measure of atrophy, we correlated gray matter volume of the epileptogenic HC and presence/absence of mesial temporal lobe sclerosis (MTS) with memory change scores.

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\(^1\) In various phases of these analyses, we used probabilistic maps (e.g., FreeSurfer, Marina) or pre-defined ROIs (e.g., from Andrews-Hanna et al) to define the hippocampus. We recognize that all are subject to some error that, in the main, likely include some small components of parahippocampal cortex for individual subjects. Nonetheless, in the interest of clarity, we will refer to the region we assessed throughout this paper as the hippocampus as the vast majority of voxels in these masks/ROIs arises from hippocampus proper.
in the WWR and WFR. Unfortunately, our patient sample was not large enough in order to perform a regression analysis with multiple predictors.

### 3.4 Results

#### 3.4.1 DMN Disruptions in Patients with mTLE

As expected, we found symmetrical DMN connectivity in healthy participants; however, in patients with mTLE, connectivity between PCC and the epileptogenic HC did not survive the applied threshold (see Figure 3.2). In both patient groups, the ipsilateral temporal pole also was disconnected from the rest of the DMN. This was confirmed by a direct contrast between healthy participants and patients: controls a) had stronger PCC-left hippocampus (lHC, t=2.52, p=0.008) and PCC-left temporal pole (lTempP, t=2.04, p=0.024) connectivity compared to patients with left mTLE, and b) stronger PCC-right temporal pole (rTempP, t=2.01, p=0.026) connectivity than patients with right mTLE. PCC-right hippocampus was a trend (rHC, t=1.48, p=0.073), indicating stronger connectivity for controls than patients with right mTLE.

Using graph-analytic measures (Bullmore and Sporns 2009), we aimed to characterize the DMN without a prior defined seed, which allows an unbiased examination of the entire network. As illustrated in Figure 3.2, there was no difference between the degree of the left and right HC in controls (t=0.83, p=0.42), however, in both patient groups, the damaged HC had a smaller degree than the contralateral HC (left mTLE: t=2.15, p=0.023; right mTLE: t=2.03, p=0.028). No other ROI showed this pattern (see Figure 3.3 for degree distribution), underlining the sensitivity of graph-analytic measures to detect focal damage in mTLE, even in such a small network. As expected, the PCC was highest in degree in all groups with no difference between healthy participants and patients with left (ANOVA, F=1.84, p=0.149) and right mTLE (ANOVA, F=1.13, p=0.342).
Figure 3.2: DMN Connectivity in Healthy Controls and Patients with mTLE

Panel A displays functional connectivity between bilateral PCC and 18 ROIs within the DMN for each group. Regions in opaque green indicate that the correlation strength survived the applied threshold of 0.05, FDR, whereas regions in transparent green indicate that the correlation strength did not survive this threshold.

Panel B displays the degree of left and right PCC and HC for each group. In controls (middle), there was no difference between the degree for left and right HC. In patients with left mTLE (left), the left HC had a smaller degree than the right HC, and in patients with right mTLE (right), the right HC had a smaller degree than the left HC (*indicates p<0.05).

ROIs: 1. lHC and 2. rHC=left and right hippocampus, 3. lPHC and 4. rPHC=left and right parahippocampal cortex, 5. lRsp and 6. rRsp=left and right retrosplenial cortex, 7. lIPL and 8. rIPL=left and right inferior parietal lobule, 9. vmPFC=ventromedial prefrontal cortex, 10. dmPFC=dorsomedial prefrontal cortex, 11. lTempP and 12. rTempP=left and right temporal pole, 13. lLTC and 14. rLTC=left and right lateral temporal cortex, 15. lTPJ and 16. rTPJ=left and right temporoparietal junction, 17. lamPFC and 18. ramPFC=left and right anterior prefrontal cortex, and PCC=posterior cingulate cortex.
Figure 3.3: Degree Distribution for all DMN Regions

Bar graphs show the degrees for each ROI per group. Bilateral HC and PCC are also displayed in Figure 3.2. L = left, R = right, *= p<0.05 two-tailed, paired t-test, ** = because of our apriori hypothesis that the damaged HC should have a smaller degree than the contralateral HC, we applied a significance threshold of p<0.05 one-tailed, paired t-test for the HC ROIs. All other ROIs were tested using two-tailed, paired t-tests. Please find ROI abbreviations in Table 3.2.

Figure 3.4: Hierarchical Clustering of DMN Connectivity

This figure displays hierarchical cluster analyses (see Andrew-Hanna et al. 2010 for methods) performed to examine differences in DMN subsystems for healthy participants and patients with left and right mTLE. In healthy participants, two subsystems emerged that replicate the DMN substructure in Andrews-Hanna et al. (2010). However, in patients with mTLE this substructure was disrupted, indicating wide-spread effects on functional connectivity within the DMN of mTLE despite a localized MTL damage. Please find full names and locations of the ROIs in Table 3.2.
3.4.2 Presurgical Status of PCC-HC Connectivity and Memory

Focusing on PCC-HC connectivity (see Figure 3.5 for whole brain analysis), we found that patients with mTLE, compared to controls, not only showed a decrease in PCC connectivity to the epileptogenic HC but also increased connectivity to the contralateral HC (see Figure 3.6, and Figure 3.9 for scatter plots of functional connectivity values).

This finding led us to inquire whether PCC-HC connectivity indexes episodic memory capacity in these patients. In controls, connectivity from the PCC to both HC indicated better verbal memory (lHC: \( r=0.61, \) MNI -31,-6,-22; rHC: \( r=0.57, \) MNI 26,-9,-15). Of note, many of the controls performed at ceiling on the WWR which might influence correlation results (see Table 3.1). In contrast, controls were not at ceiling on the WFR and only PCC-rHC connectivity correlated with non-verbal memory \((r=0.69, \) MNI 20,-11,-20).

In patients with left mTLE, stronger presurgical PCC-lHC connectivity indicated better presurgical verbal memory \((r=0.72, \) MNI -35,-33,-5), whereas PCC-rHC did not correlate with the WWR covariate. In patients with right mTLE greater PCC-rHC connectivity was associated with better non-verbal memory \((r=0.73, \) MNI 37,-25,-9), whereas PCC-lHC did not correlate with the WFR covariate.

3.4.3 Prediction of Postsurgical Memory Change

Figure 3.7 illustrates significant correlations between presurgical PCC-HC connectivity and postsurgical episodic memory change for patients with mTLE (see also Figure 3.9 for scatter plots of functional connectivity values). In left mTLE, greater PCC-IHC connectivity indicated greater memory decline \((r=-0.72, \) MNI -27,-35,9), reflecting functional adequacy of the to-be-resected tissue. Interestingly, greater connectivity to the contralateral HC (i.e., PCC-rHC), was associated with less or no postsurgical memory decline \((r=0.89 \) MNI 25,-23,-11), indicating the functional reserve of the contralateral HC to cope with surgery.

The same pattern was seen in patients with right mTLE: Increased PCC-rHC connectivity was associated with better presurgical non-verbal memory performance and also greater memory decline following surgery \((r=-0.80 \) MNI 27,-29,-9). Increased connectivity to the contralateral HC, PCC-IHC, was associated with less or no postsurgical memory decline in patients with right mTLE \((r=0.65 \) MNI -21,-17,-15).
Figure 3.5: PCC-to-Voxel Connectivity in Healthy Controls and Patients with mTLE

Panel A displays functional connectivity between the seed, PCC, and all other voxels of the brain for healthy participants, patients with left mTLE and right mTLE at a threshold of p<0.05, FDR. Only positive correlations are shown.

Panel B displays the contrast between patients with left and right mTLE versus healthy participants for functional connectivity from the PCC, thresholded at p<0.05, FDR. Regions in red indicate stronger connectivity in patients than in healthy participants; regions in blue indicate stronger connectivity in healthy participants than patients.
Figure 3.6: Presurgical Status of PCC-HC Connectivity and Episodic Memory Capacity

The upper row displays differences in PCC-HC connectivity between patients with left (A) and right (B) mTLE versus healthy participants, thresholded at p<0.05, svc. Cold colours indicate decreased and warm colours increased PCC-HC connectivity in patients in comparison to healthy controls.

The lower row displays positive correlations between PCC-HC connectivity and presurgical memory performance for left (A) and right (B) mTLE patients (p<0.05, svc). Note, the correlation values from the voxelwise analysis are shown on T1-weighted brain image; no further statistics were performed on extracted data which are plotted here for illustrative purposes. The coloured dots in the scatterplots refer to the subset of mTLE patients that underwent epilepsy surgery and continue to be part of the following figures.
Figure 3.7: Prediction of Postsurgical Episodic Memory Change

The upper row displays negative correlations between PCC connectivity to the epileptogenic HC and postsurgical memory change for left (A) and right (B) mTLE patients (p<0.05, svc). The lower row displays positive correlations between PCC connectivity to the contralateral HC and postsurgical memory change for left (A) and right (B) mTLE patients (p<0.05, svc). Again, the correlation values from the voxel-wise analysis are shown on T1-weighted brain image; no further statistics were performed on extracted data which are plotted here for illustrative purposes.
Figure 3.8: Postsurgical Status of PCC-HC Connectivity and Episodic Memory

The upper row displays increases in postsurgical, in comparison to presurgical, PCC connectivity to the remaining HC in patients with left (A) and right (B) mTLE (p<0.05, svc). The black ellipses indicate the side of epilepsy surgery. The lower row displays positive correlations between postsurgical PCC-HC connectivity and postsurgical memory performance for left (A) and right (B) mTLE patients (p<0.05, svc). Again, the correlation values from the voxelwise analysis are shown on T1-weighted brain image; no further statistics were performed on extracted data which are plotted here for illustrative purposes.
3.4.4 Postsurgical Status of PCC-HC Connectivity and Memory

Based on the findings above, we hypothesized that PCC connectivity to the contralesional HC would become more important in the support of episodic memory following surgery. Accordingly, in patients with MTL resection, connectivity between the PCC and the remaining HC increased in comparison to presurgical connectivity (see Figure 3.8). Strong correlations were found between PCC-contralateral HC connectivity and lateralized memory performance in both groups: $r=0.91$ MNI $24,-33,-4$ for WWR in left mTLE patients and $r=0.82$ MNI $-20,-10,-18$ for WWF in right mTLE patients.

**Figure 3.9: Spread of Functional Connectivity Values**

The left column displays differences in PCC-IHC and PCC-rHC connectivity between patients with left (A) and right (C) mTLE and healthy controls. The right column displays differences in PCC-HC within the contralateral hemisphere pre- and postsurgical for left (B) and right (D) mTLE patients. Individual values are extracted from the peak coordinates of the group differences established from the analyses described in the main text. Peak MNI coordinates were A: lHC= -25 -33 9, rHC= 31 -37 3, B: rHC= 30 -28 -8, C: lHC= -33 -27 -11, rHC= 25 -5 -25, and D: lHC= 20 -14 -18 No secondary significance testing was done on these scatter plots. Note that these connectivity values are z-transformed correlation coefficients, therefore shifted to a mean of 0 at the group level over the whole brain.
3.4.5 Comparison between Standard Predictors and PCC-HC Connectivity

Although we found the expected group differences for episodic memory measures and HC volume reductions (see Table 3.1), PCC-HC connectivity indicated postsurgical memory change more accurately than presurgical memory performance and structural MTL integrity (see Table 3.3). In fact, none of the standard predictors showed any significant correlations with postsurgical memory change. While the null finding for those predictors is likely a function of the small sample size, these results underscore the substantial effect size associated with connectivity.

Table 3.3: Comparison between Standard Predictors and PCC-HC Connectivity

<table>
<thead>
<tr>
<th></th>
<th>Left mTLE</th>
<th>Right mTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: Postsurgical change</td>
<td>WWR</td>
<td>WFR</td>
</tr>
<tr>
<td><strong>Functional adequacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictors: PCC-HC</td>
<td>-0.72</td>
<td>-0.80</td>
</tr>
<tr>
<td>MTS +/+&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-0.58</td>
</tr>
<tr>
<td>HC volume</td>
<td>-0.33</td>
<td>-0.44</td>
</tr>
<tr>
<td>Presurgical memory&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.37</td>
<td>-0.56</td>
</tr>
<tr>
<td><strong>Functional reserve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictors: PCC-HC</td>
<td>0.89</td>
<td>0.65</td>
</tr>
<tr>
<td>MTS +/+&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HC volume</td>
<td>-0.10</td>
<td>-0.32</td>
</tr>
<tr>
<td>Presurgical memory&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Summary of Pearson’s r between postsurgical memory change and various predictors. Correlations between PCC-HC connectivity and postsurgical memory change are significant based on previous statistical analysis. None of the other correlations reached significance (p<0.05). Predictors of functional adequacy assess parameters of the epileptogenic hemisphere, whereas predictors of functional reserve assess parameters of the contralateral hemisphere.

<sup>a</sup> MTS = mesial temporal lobe sclerosis, + = presence, - = absence
<sup>b</sup> Presurgical memory performance on the WWR for left mTLE and WFR for right mTLE
<sup>c</sup> Only 2 patients had normal MRI
3.5 Discussion

Here, we report that resting state connectivity between two key regions of the DMN, PCC and HC, reflects episodic memory capacity in such a robust manner that it shows substantial promise as a clinical indicator of memory capacity and the potential to assess cognitive morbidity in mTLE patients following epilepsy surgery. Specifically, stronger PCC connectivity to the epileptogenic HC was associated with greater loss of memory function postsurgically, indicating the functional adequacy (i.e., material-specific memory capability) of the to-be-resected tissue. These results, although somewhat preliminary due to the relatively small sample size and short follow-up, complement and extend previous findings relating measures of local structure (Rausch 1987), function (Bonelli, Powell et al. 2010) and connectivity (Wagner, Frings et al. 2007; Doucet, Osipowicz et al. 2012) to memory performance by showing that long-range connectivity among important memory structures, including regions outside the MTL, reflects the full functional capacity of the episodic memory system. In particular, we show for the first time that connectivity between the PCC and the contralateral HC was associated with less postsurgical memory decline, therefore indicating the functional reserve of the episodic memory system. While current uses of fMRI in the prediction of memory decline postsurgically focus exclusively on functional adequacy of the to-be-resected MTL (Wagner, Frings et al. 2007; Bonelli, Powell et al. 2010) or in some cases suggest that contralateral MTL activation might represent pathological plasticity (Powell, Richardson et al. 2007), we know from early epilepsy surgery reports (Penfield and Milner 1958) and intracarotid amytal procedure (Chelune 1995) that the assessment of functional reserve of eloquent non-epileptic regions is as important for the accurate prediction of postsurgical memory decline. The crucial role of PCC connectivity to the contralateral HC for functional reserve is further corroborated by our findings that this connection increases and strongly supports memory performance following surgery in the same patients. Two imaging studies that have examined neuroplasticity after epilepsy surgery found compensatory fMRI activation contralateral to the resection site (Hertz-Pannier, Chiron et al. 2002; Cheung, Chan et al. 2009). However, ours is the first study to evaluate postsurgical functional connectivity and its relation to behaviour.
Our finding of decreased PCC connectivity to the affected MTL in patients with mTLE is in line with several other fMRI resting state studies examining DMN connectivity in this patient population (Zhang, Lu et al. 2010; Liao, Zhang et al. 2011; Pittau, Grova et al. 2012). However, in contrast to our finding of increased PCC connectivity to the contralateral HC, Pittau et al., (2012) found decreased connectivity between the contralateral HC and the DMN. Whereas Pittau et al., (2012) seeded from the HC and used the entire anatomical structure as one ROI, we used a seed region outside the primary damaged regions, the PCC, and could therefore examine changes in connectivity to every voxel within the HC. Using this approach, we might have been able to detect local increases in functional connectivity within the HC that might have been lost if seeding from the entire HC as one structure.

Alzheimer’s Disease (AD) represents another patient population in which the relationship of DMN connectivity and memory is being explored. Here, there are widespread DMN alterations that relate to various clinical measures, including disease severity and level of memory impairments (Buckner, Sepulcre et al. 2009; Damoiseaux, Prater et al. 2011; Westlye, Lundervold et al. 2011). Of note, many of these studies indicate increased connectivity in preclinical and early stages of the disease, particularly between retrosplenial/posterior cingulate cortex and medial temporal regions. A recent model suggests that high neuronal activity in ‘hubs’ such as PCC may promote degeneration and in that sense heightened connectivity may have a detrimental causal role in AD pathology (de Haan, Mott et al. 2012). These findings emphasize the importance of examining functional connectivity among brain regions that reflect the specific cognitive deficits in a given patient population to evaluate the functional integrity and capacity of cognitive networks.

We found that PCC-HC connectivity indicates the functional capacity of the DMN with respect to memory performance. Due to its established functional (Fransson and Marrelec 2008; Buckner, Sepulcre et al. 2009) and structural (Hagmann, Cammoun et al. 2008; Honey, Sporns et al. 2009) key role within the DMN, and the large number of different cognitive tasks that activate this region of the brain (McDermott, Szpunar et al. 2009; Sestieri, Corbetta et al. 2011), it has been suggested that the PCC flexibly integrates information from different functional networks (Leech, Braga et al. 2012). Therefore, while the focus on the hippocampus in the assessment of functional adequacy and functional reserve in patients with mTLE is certainly justified given the nature of epilepsy surgery (Mintzer and Sperling 2008); greater emphasis on connectivity
starting from the PCC might reveal how brain regions interact to support episodic memory and possibly other cognitive abilities in both healthy and disordered brains.

3.6 Conclusions

Our findings support the idea that intrinsic connectivity reflects behavioural capacities which is a crucial step towards establishing the clinical utility of fMRI resting state to assess cognitive abilities in patients with neuropsychiatric or neurological disorders. Notably, this measure does not depend on the participant engaging in a particular task during scanning and is unaffected by potential confounds such as levels of task performance. Our findings provide substantial optimism that this connectivity metric may become an important biomarker, such that with establishment of cut-off values that capture appropriate levels of sensitivity and specificity for memory change, we may finally have a functional neuroimaging measure that can be incorporated into standard clinical practice in mTLE surgery, and perhaps other neurological and neurosurgical settings.
4 Linking DMN Connectivity to Episodic Memory Capacity: What can we learn from Patients with Medial Temporal Lobe Damage

This chapter is under review for publication:

Cornelia McCormick, Andrea B. Protzner, Alexander J. Barnett, Melanie Cohn, Taufik A. Valiante, Mary Pat McAndrews (under review)
4.1 Abstract

Computational models predict that focal damage to the Default Mode Network (DMN) causes widespread decreases and increases of functional DMN connectivity. How such alterations impact functioning in a specific cognitive domain such as episodic memory remains relatively unexplored. Here, we show in patients with unilateral medial temporal lobe epilepsy (mTLE) that focal structural damage leads indeed to specific patterns of DMN functional connectivity alterations, specifically decreased connectivity between both medial temporal lobes (MTLs) and the posterior part of the DMN and increased intrahemispheric anterior-posterior connectivity. Importantly, these patterns were associated with better and worse episodic memory capacity, respectively. These distinct patterns, shown here for the first time, suggest that a close dialogue between both MTLs and the posterior components of the DMN is required to fully express the extensive repertoire of episodic memory abilities.
4.2 Introduction

A central tenet of the Human Brain Connectome project, which aims to accurately map the structural connectivity of the human brain, is that this structural architecture allows for rich functional network dynamics to unfold and these, in turn, enable an extensive repertoire of behaviors (Sporns, Tononi et al. 2005; Sporns 2013). Whereas many studies have begun to define the relationship between structural and functional connectivity (Honey, Sporns et al. 2009; Evans 2013), the link to cognition, especially on a network level, is still relatively unexplored. In the current study we address this major gap by examining how focal structural damage affects functional connectivity and how these disruptions map onto the specific cognitive deficit.

One of the striking findings of the research on brain connectivity is the establishment of the Default Mode Network (DMN), comprising posterior cingulate, medial prefrontal, and lateral parietal cortices, as well as the medial temporal lobes (MTLs), as a large-scale neurocognitive network and part of the core architecture of the brain (Raichle, MacLeod et al. 2001; Hagmann, Cammoun et al. 2008; Mesulam 2012). Various neuroimaging techniques, including structural and functional magnetic resonance imaging (s/fMRI), have shown that nodes of the DMN are structurally and functionally highly interconnected with one another (Hagmann, Cammoun et al. 2008; Honey, Thivierge et al. 2010; Evans 2013; Hosseini and Kesler 2013). Further underscoring its centrality in the human brain, computational models predict that damage to DMN members cause widespread disruptions of functional connectivity within and beyond the DMN (Alstott, Breakspear et al. 2009). Specifically, these models predict that focal damage to the DMN causes decreased interhemispheric connectivity but increased intrahemispheric functional connectivity.

Of interest in the context of cognition, the DMN overlaps extensively with regions typically activated during autobiographical memory retrieval and has been suggested as a general recollection network (Spreng and Grady 2010; Rugg and Vilberg 2013). It is not surprising therefore that patients with widespread DMN damage, as for example in Alzheimer’s disease, suffer from severely impaired episodic autobiographical memory function (Buckner, Andrews-Hanna et al. 2008). In contrast, patients with unilateral medial temporal lobe epilepsy (mTLE)
offer the opportunity to study the impact of focal DMN pathology, as epileptic seizures arise only from the medial temporal lobe (MTL). Moreover, patients with mTLE have a neuropsychologically selective impairment on episodic memory tasks, involving verbal memory (VM) with left and visuospatial memory (VSM) with right mTLE (Milner 1972; Bell, Lin et al. 2011), and involving detailed autobiographical memory retrieval with either left or right-sided foci ((St-Laurent, Moscovitch et al. 2009), see for a review (McAndrews and Cohn 2012)).

There exist only a few studies that examine the relationship between unilateral MTL damage and functional connectivity within the DMN, and even fewer relating functional connectivity changes to specific neuropsychological profiles. For example, functional connectivity changes seen in mTLE (described below) can be attributed to changes in grey matter volume in constituent regions (Voets, Beckmann et al. 2012; Holmes, Yang et al. 2013). Further, linking functional connectivity to episodic memory capacity, we showed in an earlier study that stronger connectivity between the posterior cingulate cortex and the hippocampus (PCC-HC) on the epileptogenic side was associated with better material-specific memory capacity, and with greater postsurgical memory decline (McCormick, Quraan et al. 2013). In agreement with the idea that network integrity reflects cognitive capacity more accurately than focal integrity, the correlation between PCC-HC connectivity and episodic memory capacity was stronger than the relationship between hippocampal volume and episodic memory (i.e., focal structural integrity) and stronger than the relationship between hippocampal fMRI activation and episodic memory capacity (i.e., focal functional integrity as reported by (Bonelli, Powell et al. 2010)). Nonetheless, our previous study only focused on a single connection, PCC-HC, neglecting the overall functional status of the DMN. Whereas no study has yet related whole DMN integrity to episodic memory capacity to our knowledge, alterations of DMN connectivity and other functional networks underlying memory have been shown in mTLE (Addis, Moscovitch et al. 2007; Zhang, Lu et al. 2010; Protzner and McAndrews 2011; Pittau, Grova et al. 2012; Cataldi, Avoli et al. 2013). Importantly, those networks are not only characterized by connectivity decreases but also increases (Addis, Moscovitch et al. 2007; Bettus, Bartolomei et al. 2010; Morgan, Rogers et al. 2011; Maccotta, He et al. 2013; McCormick, Quraan et al. 2013) as predicted by virtual focal lesions to the DMN in computational models (Alstott, Breakspear et al. 2009). For example, whereas healthy controls rely on an hippocampal-centric effective network during autobiographical memory retrieval, patients with left mTLE bypass the affected
hippocampus relying instead on increased intrahemispheric connectivity between posterior retrosplenic cingulate and anterior prefrontal cortices (Addis, Moscovitch et al. 2007).

Taken together, these studies suggest the following hypotheses: (1) focal structural damage to the medial temporal lobe causes widespread DMN connectivity alterations; (2) those alterations follow a specific pattern that can be characterized by decreased interhemispheric connectivity and increased intrahemispheric connectivity; and (3) altered DMN patterns will reflect patient-specific episodic memory capacity.

4.3 Materials and Methods

4.3.1 Participants

We included 101 participants in this study: 32 patients with right mTLE, 32 with left mTLE and 37 healthy participants. All participants gave written consent to this study which was approved by the UHN Research Ethics Board. Each patient had a diagnosis of unilateral mTLE based upon localization of seizure focus to the MTL during extended EEG and video monitoring. Presence of mesial temporal lobe sclerosis (MTS) was determined by a neuroradiologist at our epilepsy clinic (see Table 4.1).

4.3.2 Verbal and visuospatial memory components

For all patients, we calculated verbal (VM), visuospatial memory (VSM) and intelligence quotient (IQ) scores based on a previously described principal component analysis (PCA) from our lab (see detailed description in (St-Laurent, McCormick et al. 2013)). In short, PCA was performed to reduce and summarize the number of measures obtained from extensive neuropsychological testing on 56 presurgical mTLE candidates (28 Right mTLE and 28 Left mTLE). Verbal memory measures included the Warrington Recognition Memory Test – Words (Warrington 1984), and two measures from the Rey Auditory Verbal Learning Test(Strauss, Sherman et al. 2006): a) the total number of recalled words over five trials and b) the percentage of words learned during the study phase that were recalled after a 20 min delay. Visuospatial memory measures included the Warrington Recognition Memory Test – Faces (Warrington
1984), the total number of designs reproduced over five learning trials on the Rey Visual Design Learning Test (Spreen and Strauss 1991) and the total number of trials to reach the learning criteria from the Spatial Conditional Associative Learning task (Petrides 1985; Taylor, Saint-Cyr et al. 1990). IQ measures included the Verbal and Performance IQ from the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). PCA on the z-transformed test scores revealed three latent components that reflected a) verbal memory, b) visuospatial memory, and c) IQ. For the current study, individual test scores were z-transformed to the original 56 patients’ distribution and PCA scores were calculated for each component by summing the product of each test’s Z-score and its corresponding coefficient. As expected, we found a material specific deficit in these patients, i.e., patients with left mTLE in comparison to patients with right mTLE had lower PCA scores on the verbal memory component (t= 2.4, df= 62, p= 0.01) but higher PCA components on the visuospatial memory component (t= 1.9, df= 62, p=0.03). In line with the view that the MTL is less pivotal for intelligence, the full scale Wechsler IQ of the patients fell well within the healthy range of the standard distribution (Left mTLE, IQ= 101.7 +/-11.6; Right mTLE IQ= 102.4 +/-12.4) and PCA scores of IQ did not differ between both patient groups (t=0.4, df= 62, p=0.68).

Table 4.1: Demographical and Clinical Information (Study 2)

<table>
<thead>
<tr>
<th></th>
<th>L-mTLE (n=32)</th>
<th>R-mTLE (n=32)</th>
<th>Controls (n=37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
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<td>15/17</td>
<td>19/18</td>
<td></td>
</tr>
<tr>
<td>handedness, right/left/ambidextrous</td>
<td>28/3/1</td>
<td>28/4/0</td>
<td>33/4/0</td>
<td></td>
</tr>
<tr>
<td>Age at scan, mean (SD)</td>
<td>36.5 (10.6)</td>
<td>37.7 (12.4)</td>
<td>35.1 (11.0)</td>
<td>0.65a</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
<td>15.2 (2.8)</td>
<td>13.5 (3.1)</td>
<td>15.9 (4.6)</td>
<td>0.03ad</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS</td>
<td>22</td>
<td>20</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>other MRI lesions</td>
<td>3</td>
<td>8</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Age of onset, mean (SD)</td>
<td>19.9 (13.3)</td>
<td>19.2 (14.1)</td>
<td>-</td>
<td>0.83b</td>
</tr>
<tr>
<td><strong>Behavioural data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verbal memory scores, mean (SD)</td>
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<td>0.20 (1.0)</td>
<td>-</td>
<td>0.01c</td>
</tr>
<tr>
<td>visuospatial memory scores, mean (SD)</td>
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<td>-0.60 (1.0)</td>
<td>-</td>
<td>0.03c</td>
</tr>
<tr>
<td>IQ scores, mean (SD)</td>
<td>0.26 (1.1)</td>
<td>0.12 (1.5)</td>
<td>-</td>
<td>0.68b</td>
</tr>
</tbody>
</table>

MTS= Medial temporal lobe sclerosis; Other MRI lesions for L-mTLE: 1 patient with left temporal pole dysembryoplastic neuroepithelial tumor (DNET), 1 with left occipital cavernoma and 1 with a single heterotopion in the occipital lobe. R-mTLE: 1 patient with small posterior temporal cavernoma, 6 with amaygdala dysplasias, and 1 with parahippocampal dysplasia

a = ANOVA; b = two-sided t-test; c = one sided t-test
d = Post hoc t-test revealed controls have more education years than patients with R-mTLE
4.3.3 MRI acquisition

We acquired an anatomical MR image and six minutes of resting state fMRI for each participant. Participants were asked to let their mind wander and relax during scanning.

All MRI data were acquired on a 3T Signa MR System (GE MedicalSystems, MilwaukeeWI). The anatomical scans consist of a T1-weighted sequence, 146 slices, 220mm FOV, 1mm slice thickness, voxelsize 0.86x0.86x1mm, 0 gap. T2*-weighted functional data were acquired in an interleaved order, between 28 and 32 slices to cover the whole brain, 240mm FOV, 5mm slice thickness, voxel size 3.75x3.75x5mm, 0 gap, TE=30msec, TR=2sec. fMRI data were taken in an oblique orientation, with each slice being perpendicular to the long axis of the hippocampus. Patient and control MRI data were acquired between 2007 and 2013.

4.3.4 Regions of interest

We included 20 ROIs (8mm spheres) based on coordinates specified in a recent comprehensive analysis of the DMN (Andrews-Hanna, Reidler et al. 2010). These were the same ROIs as used in the first study (see Table 3.2 for all ROIs and MNI coordinates).

4.3.5 fMRI preprocessing and functional connectivity matrices of the DMN

All MRI data were preprocessed using the software package SPM8 (Statistical Parametric Mapping 8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The first three frames of each fMRI session were dropped to allow signal equilibrium. Then, anatomical and functional images were reoriented to the anterior commissure and coregistered to the anatomical MNI T1 template. The anatomical images were segmented and normalized to the MNI T1 template. Functional data were realigned and unwarped, and spatially normalized to the MNI T1 template using the normalization parameter created by the segmentation process. Further, fMRI data were smoothed with a full width half maximum (FWHM) of the Gaussian smoothing kernel of 8x8x8mm. The data were temporally bandpass filtered (0.01 to 0.1 Hz) and corrected for head motion (i.e., six head motion regressors from SPM realignment procedure), white matter and ventricular signal using the conn toolbox (http://www.nitrc.org/projects/conn).

To create functional connectivity (FC) matrices, time series of voxels within each of the 20 ROIs were averaged and correlated with the averaged time series of all other ROIs resulting in 190
correlation coefficients which were then transformed using Fisher’s z calculation. Functional connectivity matrices were extracted using the conn toolbox.

4.3.6 Voxel-based morphometry and GMV of the DMN

Voxel-based morphometry (VBM) analysis was performed using the default protocol for the VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm/). The T1 images were spatially normalized using the high-dimensional DARTEL normalization and segmented into grey matter, white matter and cerebrospinal fluid. Further, non-linear effects of the normalization were modulated so that grey matter volume (GMV) values describe the amount of grey matter relative to the voxel size. For example, if two grey matter voxels are squeezed into a single voxel, then the modulated value would be two because one normalized voxel would describe two grey matter voxels in native space. Further, sample homogeneity and segmentation results were examined to identify any outliers in the study sample but no images required exclusion. As a final step, modulated images were smoothed with a FWHM of the Gaussian smoothing kernel of 8x8x8mm.

We then extracted the averaged, relative GMV after correcting for different brain size from the same 20 ROIs as described above for each participant.

4.3.7 Statistical analyses

4.3.7.1 GMV and FC Partial least squares analysis

We examined patterns of differences in FC and GMV between healthy controls and patients with mTLE, using partial least squares analyses. Detailed descriptions of PLS analysis can be found elsewhere (McIntosh, Bookstein et al. 1996; Krishnan, Williams et al. 2011). In brief, PLS uses singular value decomposition (SVD) to extract ranked latent variables (LVs) from the covariance matrix of brain data and experimental groups. For the current study, the brain data matrices for the FC-PLS contained 190 correlation coefficients (every possible connection between the 20 DMN ROIs) per subject and were grouped into healthy controls and patients with left and right mTLE. For the GMV-PLS, brain data matrices contained 20 GMV values from the 20 DMN ROIs per subject and were grouped again into healthy controls and patients with left and right mTLE. The resulting LVs express patterns of brain data (e.g., strength of FC or amount of relative GMV) associated with each group. Statistical significance of the LVs was assessed using
permutation testing. In this procedure, each subject’s data was randomly reassigned (without replacement) to different experimental groups, and a null distribution was derived from multiple permuted solutions. In the current experiment, we used 500 permutations and considered LVs as significant if $p < 0.05$. Further, we assessed the reliability of each brain data entry that contributed to a specific LV’s pattern using a bootstrap estimation of the standard error (i.e., bootstrap ratio, BSR). In this scenario, subjects were sampled randomly (100 times in total) with replacement and a new analysis was performed. In Table S2, we report BSRs greater than 2.00 for the FC-PLS and BSRs greater than 3.00 for the GMV-PLS. Additional information derived from PLS analyses are brain scores (i.e., similar to factor scores) for each individual that indicate the extent to which an individual expresses the pattern represented by the LV.

4.3.7.2 GMV-EM and FC-EM Partial least squares

We examined whether functional connectivity or GMV of the DMN correlates with episodic memory measures in patients with mTLE, using a different version of PLS. This version examines the relationship between a behavioral measure, in our case episodic memory scores, and brain data as a function of the experimental group (Krishnan, Williams et al. 2011). The general difference to the previous PLS version is that, here, the covariance matrix used for SVD stems from correlation values between the behavioral measure (i.e., episodic memory capacity) and all other entries in the brain data matrix (i.e., rather than brain data matrices per group). For our GMV-VM/VSM and FC-VM/VSM-PLS, brain data matrices consisted again either of 20 GMV values or 190 FC values per patient, respectively. GMV and FC matrixes were correlated with behavioural measures, including verbal (VM), visuospatial (VSM) memory and IQ scores. To capture a greater variability of episodic memory performance, we concatenated across patients with left and right mTLE. Again, we used 500 permutations to assess significance of the LV and 100 bootstrap samples to assess reliable patterns. We considered functional connections (FC-EM-PLS) or ROIs (GMV-EM-PLS) with a BSR greater than 2.00 reliable.

4.3.7.3 Mediation analysis

To examine whether the influence of structural damage on episodic memory capacity is mediated by functional connectivity, we conducted a mediation analysis using the Aroian test (Aroian 1944). In short, the Aroian test examines whether the unstandardized regression coefficient between the independent variable (i.e., structural integrity) and the dependent variable (i.e.,
episodic memory scores) decreases significantly if the mediator variable (i.e., functional connectivity) is included in the prediction model. Specifically, we conducted a series of simple and multiple linear regressions 1. between brain scores from the GMV-VM/VSM-PLS and episodic memory scores, 2. between brain scores from the FC-VM/VSM-PLS and episodic memory scores, 3. between brain scores from the GMV-VM/VSM-PLS and FC-VM/VSM-PLS analyses, and 4. between both GMV-VM/VSM-PLS and FC-VM/VSM-PLS brain scores and episodic memory. We then entered the unstandardized regression coefficients and standard errors of regression analysis 3 and 4 into the Aroian test. We considered a decrease of the regression coefficients of $p < 0.05$ significant. Of note, both GMV- and FC-VM/VSM-PLS maximize the correlation between GMV or FC and episodic memory and it is therefore not surprising that both GMV and FC predict episodic memory capacity significantly. However, we are not interested in this correlation per se (as it would be considered double-dipping, see (Kriegeskorte, Simmons et al. 2009)) but in the mediating effect of functional connectivity. To test the specificity of the relationship between structural integrity, functional connectivity and episodic memory capacity, we also conducted a mediation analysis using functional connectivity as the independent and structural integrity as the mediator variable.

### 4.4 Results

#### 4.4.1 Structural damage and functional connectivity alterations of the DMN in mTLE

Patients with mTLE showed decreased grey matter volume of the ROIs situated in the affected medial temporal lobe, including the hippocampal formation and parahippocampal cortex in comparison to healthy controls (GMV-PLS, CTL and Left mTLE, $p=0.005$; CTL and Right mTLE, $p=0.002$, see Figure 4.1 for a general description of the DMN in controls and patients with mTLE). Additionally, patients with left mTLE also had decreased grey matter volume in the ROI situated in the left lateral temporal cortex and patients with right mTLE showed decreased grey matter volume in the ROI situated in the right temporal pole (see Figure 4.2 and Table 4.2). There was no ROI that showed greater grey matter volume in patients than controls. Consistent
with previous studies examining grey matter volume in mTLE (Keller and Roberts 2008), these results indicate that mTLE is associated with grey matter volume loss primarily, though not exclusively, within the medial and lateral aspect of the affected temporal lobes.

In contrast to the marked grey matter volume decline concentrated in the affected MTL, we found widespread functional connectivity alterations within the DMN in patients with mTLE in comparison to healthy controls (FC-PLS, Left mTLE p<0.001; Right mTLE p<0.009, see Figure 4.2 and Table 4.3). Interestingly, we found the same characteristic differences in both patient groups. First, in comparison to healthy controls, patients with mTLE showed reduced functional connectivity between the affected MTL and the posterior part of the DMN. That is, of the 23 connections that were significantly increased in controls relative to left mTLE patients, 11 involved ROIs of the MTL and posterior part of the DMN. A similar pattern was observed in the comparison of controls with right mTLE patients in that 6 of the 15 increased connections involved those ROIs. In contrast, very few such connections were increased in patients relative to controls (1 of 12 for left mTLE, 0 of 9 for right mTLE). Specifically, controls show strong interhemispheric connectivity between bilateral retrosplenial cortices and hippocampi, whereas patients with mTLE only had weak connectivity between these ROIs. Second, patients with mTLE showed a distinct pattern that was characterized by stronger intrahemispheric, anterior-posterior connectivity than healthy controls. Especially striking was the increased functional connectivity involving the ROIs situated in the prefrontal cortex. This was present in 7 out of 12 increased connections in left mTLE and only 2 of 23 increased connections for controls. A similar pattern was seen for right mTLE (5 of 9 connections) compared to controls (0 of 15 connections).
Figure 4.1: Functional Connectivity within the DMN in Healthy Controls and Patients with mTLE
Correlation coefficients greater than 0.7 are displayed in solid red lines. Correlation coefficients lower than 0.7 are depicted in dotted, thin red lines. The size of the nodes indicates the degree (at the threshold of 0.7). Of note, the PCC displays the greatest number of degrees in all three groups.
Table 4.2: Grey Matter Volume Differences within the DMN between Healthy Controls and Patients with mTLE

<table>
<thead>
<tr>
<th>Controls&gt; L-mTLE</th>
<th>ROI</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lHF</td>
<td>4.33</td>
</tr>
<tr>
<td></td>
<td>ILTC</td>
<td>4.26</td>
</tr>
<tr>
<td></td>
<td>IPHC</td>
<td>4.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls&gt; R-mTLE</th>
<th>ROI</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rPHC</td>
<td>4.70</td>
</tr>
<tr>
<td></td>
<td>rHF</td>
<td>4.69</td>
</tr>
<tr>
<td></td>
<td>rTempP</td>
<td>4.32</td>
</tr>
</tbody>
</table>

See Table 3.2 for full names and MNI coordinates of the ROIs. BSR = boot strap ratio

Table 4.3: Functional Connectivity Differences within the DMN between Healthy Controls and Patients with mTLE

<table>
<thead>
<tr>
<th>Controls&gt; L-mTLE</th>
<th>Connections</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lHF-IRSP</td>
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<tr>
<td></td>
<td>IPHC-rHF</td>
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</tr>
<tr>
<td></td>
<td>lHF-rHF</td>
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</tr>
<tr>
<td></td>
<td>IPCC-lTempP</td>
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</tr>
<tr>
<td></td>
<td>ILTC-lTempP</td>
<td>3.15</td>
</tr>
<tr>
<td></td>
<td>lHF-vmPFC</td>
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<td>lTempP-rPCC</td>
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<tr>
<td></td>
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<td></td>
<td>ITPJ-lTempP</td>
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<td>IRSP-rHF</td>
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<td></td>
<td>lamPFC-ramPFC</td>
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<td>rHF-rIPL</td>
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<td>lHF-IPHC</td>
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<td>rHF-rRSP</td>
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<table>
<thead>
<tr>
<th>Controls&gt; R-mTLE</th>
<th>Connections</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IIPL-ramPFC</td>
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<td>dmPFC-vmPFC</td>
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</tr>
</tbody>
</table>
See Table 3.2 for full names and MNI coordinates of the ROIs. BSR = boot strap ratio.
Blue: Connections between the MTL (HF and PHC) and the posterior part of the DMN (PCC, RSP, IPL, TPJ)
Red: Any connections that involve ROIs situated in the prefrontal cortices (vmPFC, dmPFC, amPFC)
All connections that involve the hippocampus are illustrated in bold font.
Further, linear regression analyses revealed that brain scores from the structural PLS strongly predicted brain scores of the functional connectivity PLS in both patient groups (see Figure 4.1, CTL and Left mTLE, $r^2 = 0.24$, $p < 0.001$; CTL and Right mTLE, $r^2 = 0.22$, $p < 0.001$). These findings are especially of interest because, as predicted by virtual lesions (Alstott, Breakspear et al. 2009), local structural DMN damage causes wide-spread functional connectivity alterations throughout this network. In fact, in both patient groups, these wide-spread disturbances of functional connectivity resulted in specific connectivity patterns (i.e., decreased posterior interhemispheric and increased anterior intrahemispheric connectivity).

### 4.4.2 Functional connectivity patterns related to individual differences in episodic memory capacity

We found that functional connectivity of the DMN indicated verbal (FC-VM-PLS, $p = 0.01$) and visuospatial memory capacity (FC-VSM-PLS, $p = 0.04$, see Figure 4.3 and Table 4.4 for significant connections) in this patient cohort. Strikingly, the same functional connectivity patterns that separated healthy controls from patients before were now associated with better and worse episodic memory performance in the patient groups. That is, connections associated with better verbal and visuospatial memory capacity mainly integrated the material-specific MTL into the posterior part of the DMN (VM: 5 of 7, VSM: 4 of 11 significant connections), whereas connections that were associated with impaired verbal and visuospatial memory capacity tended to be intrahemispheric connections and involve DMN nodes of the prefrontal cortex (VM: 11 of 18, VSM: 8 of 22 significant connections). Whereas the previous FC-PLS examined the central tendencies of the groups’ connectivity pattern, the current FC-VM/VSM-PLS examined individual differences and revealed that those patients who do better on clinical memory measures tend to rely on the pattern most associated with controls whereas those patients who do worse on memory testing tend to rely on the altered pattern that best characterizes the patient group as a whole. In agreement with the idea that DMN integrity indicates episodic memory capacity specifically and not other cognitive abilities, we found that DMN connectivity did not reflect intelligence scores in mTLE patients (FC-IQ-PLS, $p = 0.91$).
Figure 4.2: Structural and Functional DMN Integrity Differences between Healthy Controls and Patients with mTLE

1A. Red spheres illustrate ROIs in which patients with left (L-mTLE) and right mTLE (R-mTLE) have decreased grey matter volume (GMV) in comparison to healthy controls (CTL). Of note, there were no increases of GMV in patients with mTLE in comparison to healthy controls.

1B. Red lines illustrate differences in functional connectivity between healthy controls than patients with left and right mTLE. The line thickness indicates the boot strap ratio value.

1C. Correlation between brain scores resulting from the GM- and FC-DMN analyses in controls, R-mTLE and L-mTLE, indicating that the extent of structural DMN damage, correlates with the extend of functional DMN connectivity alterations. See ROI description below Figure 4.3.
Figure 4.3: Functional Connectivity Alterations of the DMN and Episodic Memory Capacity in Patients with mTLE

Panels 2A illustrates networks that are associated with better episodic memory capacity and panels 2B illustrates networks that are associated with worse episodic memory capacity in patients with L-mTLE and R-mTLE. Significant connections are displayed in red. The line thickness indicates the boot strap ratio value.

Panel 2 C displays the relation between brain scores (i.e., how well a participant expresses the above networks) and individual episodic memory capacity. For example, patients with higher brain scores have stronger connectivity within the network associated with better verbal memory and weaker connectivity within the pattern associated with worse verbal memory.

FC = functional connectivity. ROIs: 1. lHC and 2. rHC=left and right hippocampus, 3. lPHC and 4. rPHC=left and right parahippocampal cortex, 5. lRsp and 6. rRsp=left and right retrosplenial cortex, 7. lIPL and 8. rIPL=left and right inferior parietal lobule, 9. vmPFC=ventromedial prefrontal cortex, 10. dmPFC=dorsomedial prefrontal cortex, 11. lTempP and 12. rTempP=left and right temporal pole, 13. rLTC and 14. rLTC=left and right lateral temporal cortex, 15. lTPJ and 16. rTPJ=left and right temporoparietal junction, 17. lamPFC and 18. ramPFC=left and right anterior medial prefrontal cortex, and 19. lPCC and 20. rPCC=left and right posterior cingulate cortex.
Table 4.4: Functional Connectivity within the DMN indicates Episodic Memory Capacity in Patients with mTLE

<table>
<thead>
<tr>
<th>Verbal Memory Connections</th>
<th>BSR</th>
<th>Worse VM Connections</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHE-FIRSP</td>
<td>2.82</td>
<td>rRSP-vmPFC</td>
<td>3.99</td>
</tr>
<tr>
<td>IHE-IPCC</td>
<td>2.76</td>
<td>ITPJ-rTempP</td>
<td>3.13</td>
</tr>
<tr>
<td>IHE-IPHC</td>
<td>2.44</td>
<td>ramPFC-vmPFC</td>
<td>3.03</td>
</tr>
<tr>
<td>IHE-rIPL</td>
<td>2.20</td>
<td>rPCC-vmPFC</td>
<td>2.93</td>
</tr>
<tr>
<td>IHE-vmPFC</td>
<td>2.05</td>
<td>IRSP-vmPFC</td>
<td>2.84</td>
</tr>
<tr>
<td>lamPFC-rampFC</td>
<td>2.00</td>
<td>ILTC-rTempP</td>
<td>2.71</td>
</tr>
<tr>
<td>IHE-rPCC</td>
<td>2.00</td>
<td>lamPFC-rHF</td>
<td>2.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visuospatial Memory Connections</th>
<th>BSR</th>
<th>Worse VM Connections</th>
<th>BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITPJ-rHF</td>
<td>4.81</td>
<td>rTPJ-vmPFC</td>
<td>3.77</td>
</tr>
<tr>
<td>ILTC-rPHC</td>
<td>3.92</td>
<td>rPCC-rTempP</td>
<td>3.39</td>
</tr>
<tr>
<td>ITPJ-rPHC</td>
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<td>rPCC-vmPFC</td>
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</tr>
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<td>ITPJ-vmPHC</td>
<td>2.98</td>
<td>ILTC-IPCC</td>
<td>3.15</td>
</tr>
<tr>
<td>dmPFC-rampFC-rampFC</td>
<td>2.69</td>
<td>IPHC-rTempP</td>
<td>3</td>
</tr>
<tr>
<td>ITPJ-rHF</td>
<td>2.14</td>
<td>IPHC-vmPFC</td>
<td></td>
</tr>
<tr>
<td>ITPJ-rPHC</td>
<td>2.54</td>
<td>rPCC-rTempP</td>
<td></td>
</tr>
<tr>
<td>ITPJ-rPCC</td>
<td>2.29</td>
<td>ILTC-rPCC</td>
<td></td>
</tr>
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<td>rRSP-rTempP</td>
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<td>ITPJ-rIPL</td>
<td>2.06</td>
<td>ITPJ-vmPFC</td>
<td></td>
</tr>
</tbody>
</table>
See Table 3.2 for full names and MNI coordinates of the ROIs. BSR = bootstrap ratio.

Blue: Connections between the MTL (HF and PHC) and the posterior part of the DMN (PCC, RSP, IPL, TPJ)
Red: Any connections that involve ROIs situated in the prefrontal cortices (vmPFC, dmPFC, amPFC)
All connections that involve the hippocampus are illustrated in bold font.

As in our previous study, the connection between the PCC and the affected HC predicted better verbal and visuospatial memory capacity (McCormick, Quraan et al. 2013). Here, we extend this finding with a larger cohort of patients and refined composite memory scores rather than the single memory tests we used previously (see Figure 4.4). Of note, patients in the earlier study are a subset of the current study cohort. Comparable to the previous findings, in patients with left mTLE, connectivity from the PCC to the left HC (PCC-lHC) correlated with verbal memory scores ($r^2=0.30, p=0.001$) and in patients with right mTLE, connectivity from the PCC to the right HC (PCC-rHC) correlated with visuospatial memory scores ($r^2=0.18, p=0.015$). However, brain scores reflecting the functional integrity of the entire DMN predicted verbal and visuospatial memory capacity more accurately than PCC-HC connectivity alone (see Figure 4.5). In patients with left mTLE, DMN connectivity correlated with verbal memory scores ($r^2=0.61, p<0.001$) and in patients with right mTLE, DMN connectivity correlated with visuospatial memory scores ($r^2=0.53, p<0.001$). These results suggest that the overall integrity of the DMN is a more accurate marker for episodic memory capacity in mTLE than its individual connections.
Figure 4.4: PCC-HC Connectivity indicates Episodic Memory Capacity in Patients with mTLE
This figure shows the extension of the data published in the first study (see Figure 3.6). The upper row in each panel displays differences in PCC-HC connectivity between patients with left (A) and right (B) mTLE versus healthy participants, thresholded at p<0.05, svc. Blue indicates decreased and red increased PCC-HC connectivity in patients in comparison to healthy controls. The lower row in each panel displays positive correlations between PCC-HC connectivity and presurgical memory performance for left (A) and right (B) mTLE patients (p<0.05, svc).
Correlation between episodic memory capacity and connectivity between the PCC and damaged HC (left y-axis) and between episodic memory capacity and brain scores expressing the whole DMN integrity, as measured by FC-VM/VSM-PLS (right y-axis). Verbal memory: PCC-LHC: $r^2 = 0.30$, Brain scores: $r^2 = 0.61$; Visuospatial memory: PCC-RHC: $r^2 = 0.18$, Brain scores: $r^2 = 0.53$. DMN integrity is a better indicator of episodic memory than PCC-HC connectivity.

In contrast to the strong relationships observed in the foregoing analyses, structural integrity of the DMN as a whole did not vary with verbal (GMV-VM-PLS, $p = 0.12$) or visuospatial memory capacity (GMV-VSM-PLS, $p = 0.41$) in patients with mTLE. Given the circumscribed seizure onset in mTLE, we further investigated the structural integrity of the hippocampus itself, using different hippocampal masks including total HC volume, ROIs situated in posterior and anterior HC segments (MNI coordinates: left and right anterior hippocampal ROI $-/+28 -12 -20$; left and right posterior hippocampal ROI $-/+28 -38 -3$), and the ROI of the HC used in the current PLS analyses, to see if this could be a stronger associate of our memory scores. However, that was not the case. The majority of correlations were weak ($r^2 < 0.1$) and non-significant ($p > 0.1$), with only two regions demonstrating trends toward a relationship with verbal memory capacity (left HC, $r^2 = 0.05$, $p = 0.06$; left posterior HC $r^2 = 0.06$, $p = 0.06$).

### 4.4.3 Relationship of combined structural damage and functional connectivity alterations to predicting episodic memory capacity

As we noted earlier, our indicators of structural and functional integrity of the DMN are correlated, so we investigated whether any (albeit small) link between structural degradation and memory may be mediated by functional connectivity. A formal mediation analysis revealed this to be the case in that the unstandardized regression coefficient (i.e., B) between structural integrity (as measured by GMV-VM/VSM-PLS) and episodic memory (VM, B=8.36; VSM,
B=3.28) dropped significantly when functional connectivity (as measured by FC-VM/VSM-PLC) was taken into account (VM, B=3.06, Aroian test p<0.001; VSM, B=1.41, Aroian test p=0.029). To highlight this directional influence, examining structural integrity as the mediator did not reveal significant results (VM, Aroian test p=0.07; VSM, B=1.41, Aroian test p=0.21). Together, these findings support the idea that structural integrity shapes the possible dynamics of neuronal activity and that changing patterns of these dynamics underlie behavioral variability.

4.5 Discussion

In this study, we bring together a number of key observations that speak to the relationship between structural damage, functional connectivity and cognitive capacity. First, we found widespread functional connectivity alterations throughout the DMN that correlated with the severity of structural damage confined largely to the ipsilateral medial and lateral temporal lobe. In line with our results, previous studies also found that functional connectivity alterations can at least be in part explained by structural damage (Voets, Beckmann et al. 2012; Holmes, Yang et al. 2013). Our findings converge with other recent studies indicating that the greater the structural damage to the MTL, the poorer the integration of this region with the DMN particularly in its posterior extent (Voets, Beckmann et al. 2012).

Second, we found distinct DMN connectivity patterns that separated patients with mTLE from healthy controls, in that controls showed greater posterior interhemispheric DMN and patients with mTLE greater anterior intrahemispheric DMN connectivity. Interestingly, virtual lesion models predicted these patterns in that damage to virtual DMN nodes result in widespread decreased interhemispheric and increased intrahemispheric connectivity (Alstott, Breakspear et al. 2009). Although not affecting the DMN directly, in line with this idea is a recent study showing that complete surgical separation of the two hemispheres in monkeys disrupted interhemispheric connectivity as expected but also increased intrahemispheric connectivity (O'Reilly, Croxson et al. 2013). In mTLE, previous studies report mostly reduced functional connectivity to the damaged MTL, however, a growing number of studies also report increases of functional connectivity but these are inconsistent regarding the location and extent (Bettus,
Bartolomei et al. 2010; Morgan, Rogers et al. 2011; Maccotta, He et al. 2013; McCormick, Quraan et al. 2013). One major difference between ours and previous studies is that they typically used single seed-based analysis whereas we used a multivariate pattern analysis that allowed us to examine altered patterns throughout but specific to DMN connectivity. That is, the specification of a single seed, for example, the damaged or contralateral medial temporal lobe, only examines a subset of DMN connections; i.e., from the medial temporal lobe to all other regions of the DMN. This approach might obscure effects of extra-MTL connections within the DMN, such as the pattern we identified in patients with mTLE. On the other hand, whole brain analysis (for example, independent component analysis, ICA) might obscure effects specific to the DMN (but see (Voets, Beckmann et al. 2012) for an exception).

Third and in line with our previous observation (McCormick, Quraan et al. 2013), functional connectivity alterations of the DMN indicated episodic memory capacity reliably in patients with mTLE, but structural alterations did not. Whereas many studies have shown a direct relationship between structural integrity of the hippocampus and episodic memory (Maguire, Gadian et al. 2000; Poppenk and Moscovitch 2011), our results point to a more fundamental but indirect role of structural integrity. That is, the influence of structural DMN alteration on episodic memory capacity is mediated by alterations in functional networks. This finding is generally in line with the idea of the Human Brain Connectome project that the structural foundation of the brain enables its dynamic, functional repertoire which in turn is expressed as flexible behavior (Sporns, Tononi et al. 2005; Honey, Sporns et al. 2009; Honey, Thivierge et al. 2010; Sporns 2013).

Fourth, we show here for the first time that the whole pattern of functional DMN integrity captures between-subject variance in memory capacity better than focal activation or even one connection. This finding corroborates the idea that episodic memory capacity does not rely simply on the integrity of one region, even if that region, for example the hippocampus, is essential to episodic memory (McIntosh 2000). Instead, our data indicate that episodic memory, even as measured in a clinical setting that is expressly designed to assess memory capacity involving MTL regions, is supported by a large-scale brain network. Of course the DMN is not defined by a pattern of activation directly related to memory performance, but it is largely co-extensive with networks involved in memory retrieval such as the autobiographical memory network and recollection memory (Spreng and Grady 2010; Buckner 2012; Rugg and Vilberg
2013). Nonetheless, the extent to which our findings can be generalized to memory networks defined by such tasks and beyond patients with mTLE, in whom longstanding seizures and structural damage may result in unique patterns of plasticity or remodelling, remains to be seen.

Lastly, we observed two distinct patterns of functional connectivity alterations that separated patients with mTLE from healthy controls on one hand and that predicted better and worse episodic memory performance within this patient population on the other hand. These patterns might be best described as (1) a posterior interhemispheric network that integrates the MTL into the posterior part of the DMN and that was stronger in healthy controls and associated with better episodic memory capacity in patients and (2) an anterior intrahemispheric network that connects the prefrontal cortex with other parts of the DMN and that was stronger in patients with mTLE and associated with worse episodic memory capacity in them. While none of the current literature speaks to this distinction directly, a number of recent observations allows for some speculation. For example, recruitment of the posterior parts of the DMN and connectivity between them have been implicated in episodic memory retrieval, whereas recruitment of the anterior parts (i.e., prefrontal cortices) and connectivity between prefrontal and posterior cingulate cortices have been implicated in semantic memory retrieval (Shapira-Lichter, Oren et al. 2013). Further, we showed in an earlier study that the anterior hippocampus was strongly connected to a fronto-temporal network during the general search for an autobiographical memory, whereas bilateral posterior hippocampi were strongly connected to a widespread posterior network during the vivid, detail-rich elaboration of these autobiographical memories (McCormick, St-Laurent et al. 2013). Moreover in comparison to controls, patients with left mTLE show decreased connectivity of posterior medial regions to the left hippocampus during autobiographical memory retrieval but increased connectivity to the prefrontal cortex (Addis, Moscovitch et al. 2007). Further strengthening the idea that the interhemispheric dialogue between the medial temporal lobes is crucial for vivid autobiographical memory elaboration, patients with either left or right MTL damage are able to retrieve the general gist of autobiographical memories but impaired at recovering specific details of those experiences (St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011). Thus, the distinct patterns of connectivity revealed in our data may reflect an important aspect of the fundamental organization of human memory, in that it is the dynamic interhemispheric communication between both medial temporal lobes and the posterior part of the DMN that is most crucial for
vivid, detail-rich episodic retrieval of the kind that supports both recollection of autobiographical
details as well as recall and recognition of material in clinical measures.

4.6 Conclusions

Our findings support the idea that focal structural damage leads to widespread functional
connectivity changes. By using multivariate analysis of functional connectivity matrices, we
were able to extract functional networks within the DMN constituents that reflected differences
between patients with MTL damage and healthy controls, and were further linked to episodic
memory capacity. These patterns described here for the first time are especially interesting as
they raise new questions about the neural organization of episodic memory.
5 Functional and Effective Hippocampal-Neocortical Connectivity during Construction and Elaboration of Autobiographical Memory Retrieval

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Cornelia McCormick, Marie St-Laurent, Ambrose Ty, Taufik A. Valiante, Mary Pat McAndrews (In Press). Functional and Effective Hippocampal-Neocortical Connectivity during Construction and Elaboration of Autobiographical Memory Retrieval. Cerebral Cortex
5.1 Abstract

Autobiographical memory (AM) provides the opportunity to study interactions among brain areas that support the search for a specific episodic memory (construction), and the later experience of mentally reliving it (elaboration). While the hippocampus supports both construction and elaboration, it is unclear how hippocampal-neocortical connectivity differs between these stages, and how this connectivity involves the anterior and posterior segments of the hippocampus, as these have been considered to support the retrieval of general concepts and recollection processes, respectively.

We acquired fMRI data in 18 healthy participants during an AM retrieval task in which participants were asked to access a specific AM (construction) and then to recollect it by recovering as many episodic details as possible (elaboration). Using multivariate analytic techniques, we examined changes in functional and effective connectivity of hippocampal-neocortical interactions during these phases of AM retrieval.

We found that the left anterior hippocampus interacted with frontal areas during construction and bilateral posterior hippocampi with visual-perceptual areas during elaboration, indicating key roles for both hippocampi in coordinating transient neocortical networks at both AM stages. Our findings demonstrate the importance of direct interrogation of hippocampal-neocortical interactions to better illuminate the neural dynamics underlying complex cognitive tasks such as AM retrieval.
5.2 Introduction

Autobiographical memory (AM) retrieval involves a variety of mental processes, which include searching for and accessing specific life episodes (the construction stage), and recollecting them by reassembling vivid episodic details (the elaboration stage). These cognitive processes are supported by a number of neocortical areas as well as by the hippocampus, which might play the key role in initiating and coordinating their engagement. To date, however, there is little experimental evidence regarding the nature of this hippocampal-neocortical interplay during the different stages of AM retrieval. Here, we examine functional and effective connectivity of hippocampal-neocortical networks during AM construction and AM elaboration.

In an influential model, Conway (2009) organizes AM into nested hierarchical levels of self-knowledge, from the most conceptual and general knowledge of life periods or events (e.g., my teenage years) to the most concrete and contextually specific life episodes (e.g., the song playing during my first kiss). Memories of specific life events are unique because they contain concrete and vivid episodic elements (Conway and Pleydell-Pearce 2000; Conway 2009) which allow us to recollect past events in a vivid manner (Tulving 2002). According to this model, when an event-specific AM is prompted with a thematic cue, such as “kiss” or “party” (a typical experimental setting of AM retrieval), the first level of entry into AM knowledge is typically through memory for repeated or extended life events. In this case, one usually accesses episodic elements only after accessing more general and abstract personal knowledge. In other words, retrieving a specific autobiographical episode typically involves searching through general knowledge (akin to the construction stage), and then reliving the episode vividly by accessing episodic elements (the elaboration stage). In this sense, AM retrieval can be seen as a particular instance of cued contextually-rich episodic memory retrieval that offers the unique opportunity to study construction and elaboration processes.

Although there is very little information about how medial temporal and neocortical regions interact with one another in the different stages of AM retrieval, there are some data regarding the general regions involved in this two-process model. Based on an early study using electroencephalography, Conway speculated that a fronto-temporal network would support
construction and a more diffuse occipito-temporo-parietal network would support the multimodal re-experience of episodic elements underlying elaboration (Conway, Pleydell-Pearce et al. 2001). Although these predictions are generally supported by neuroimaging studies showing the importance of the frontal lobes to memory retrieval processes (St Jacques, Kragel et al. 2011; Addis, Knapp et al. 2012) and the importance of the visual-perceptual areas to visual imagery (Rubin and Greenberg 1998; Greenberg, Eacott et al. 2005), research focusing on the differentiation between construction and elaboration of AMs did not show the clear anterior-posterior dissociation that Conway predicted more than ten years ago (Addis DR et al 2007; Holland AC et al 2011; Rabin JS and Rosenbaum RS 2012 but see Daselaar SM et al 2008). However, none of these previous studies focused specifically on hippocampal-neocortical connectivity, although St Jacques and colleagues used independent component analysis (ICA) to identify networks involved in different phases of AM retrieval (St Jacques PL et al. 2011).

With the current work, we explored the possibility that the hippocampus might be the hub that coordinates these anterior and posterior networks during AM retrieval. This proposal is based on functional magnetic resonance imaging (fMRI) studies showing sustained hippocampal activation during AM retrieval, indicating a pivotal role for the hippocampus in both construction and elaboration (Addis, Wong et al. 2007; St Jacques, Kragel et al. 2011). Also, neuroanatomical studies show that the hippocampus is perfectly situated between and strongly connected to frontal cortices and visual-perceptual areas, i.e. all areas supposedly involved in AM construction and elaboration (Lavenex and Amaral 2000; Lavenex, Suzuki et al. 2002). Lastly, a connectivity-based neuroimaging study from our group showed that hippocampal-neocortical networks support encoding and retrieval of episodic memories (McCormick, Moscovitch et al. 2010), thus strengthening the idea that the hippocampus forms transient links between neocortical brain regions that are necessary for contextually-rich memory processing (Teyler and DiScenna 1986; Buzsaki 1996; Teyler and Rudy 2007; Rugg, Johnson et al. 2008). Here, we tested the hypothesis that hippocampal-neocortical connectivity shifts from an early hippocampal-frontal network at construction to a late hippocampal-occipito-parietal network at elaboration during AM retrieval.

Growing evidence suggests that the hippocampus can be segregated into functionally distinct segments along its long-axis (Fanselow and Dong 2010; Poppenk and Moscovitch 2011; Viard, Desgranges et al. 2012; Bonnici, Chadwick et al. 2013; Poppenk, Evensmoen et al. 2013).
Together with a recent review aimed to map different cognitive systems onto anterior and posterior memory networks (Ranganath and Ritchey 2012), this formulation suggests that the anterior part of the hippocampus, possibly in interaction with frontal areas, might support cue-specific retrieval attempts and activation of general concepts, functions that are needed for AM construction. In contrast, the posterior hippocampus might support recovery of detailed perceptually rich episodic memories through communication with visual-perceptual areas, suggesting a potential role in AM elaboration. However, experimental evidence for this dissociation remains thin, particularly in the context of AM, and so in the current study we specifically assessed anterior and posterior hippocampal connectivity.

We aimed to map both functional and effective connectivity amongst brain regions that support construction and elaboration of AM retrieval. We were specifically interested in characterizing how fronto-temporal and occipito-temporo-parietal regions interact at each phase with the anterior and posterior hippocampus, which we hypothesized to play functionally distinct roles in AM retrieval.

5.3 Materials and Methods

5.3.1 Participants
18 healthy controls (7 women, 11 men, 15 right-handed, 3 left-handed) with no history of neurological or psychiatric disorders participated in this study and gave written informed consent in accordance with a research protocol approved by the University Health Network Ethics Board. Age ranged from 22 to 61 with an average of $36.17 \pm 12.3$. This broad age range was chosen because we recruited participants age-matched to a patient group whose data are not part of the current analysis.

5.3.2 Experimental Procedure
Immediately before the scanning procedure, the experimental task was explained to the participants and they completed 6 practice trials of each condition. The contents of all retrieved
AMs were then probed to confirm that participants understood the instructions (i.e., the generated events were specific in time and place).

The experimental task consisted of two different conditions, AM retrieval and math, with 22 trials of each condition. The duration of each trial was 16.5 seconds and trials were presented in a randomized fashion, with a jittered interstimulus interval (ISI) of 0.5, 1.0, or 1.5 seconds. In the AM retrieval condition, participants were presented with an event cue such as “a party”. The participants were asked to recall a specific event from their personal past that was coherent with the cue and to press a response button once they retrieved a specific incident. During the remaining seconds of the trial, they were instructed to elaborate the details of that particular memory, and to relive the event in their mind’s eye. The button press indicated the end of the construction phase, and the beginning of the elaboration phase (see Addis DR et al. 2007 for a similar paradigm). In the math condition, participants were asked to solve a simple math problem, for example 19+4, and press a response button once they had the solution in mind. During the remaining seconds of the trial, participants were instructed to add three’s to the solution (e.g. 23 + 3 + 3…). At the end of each trial, participants were asked to rate the memory as vivid or faint and the math problem as easy or hard. Due to technical difficulties, the responses of four participants were not recorded during the task, however, in a debriefing after the scan they confirmed that they followed the instructions throughout the task and we therefore included their fMRI data in the analyses.

5.3.3 Data Acquisition

Anatomical and functional data were acquired on a 3-T Sigma MR System (GE Medical Systems, Milwaukee). Anatomical scans, for co-registration of functional data, were acquired first (T1-weighted sequence, 120 slices, FOV = 220 mm, slice thickness = 1 mm, 0 gap, 256 x 256 matrix, resulting in a voxel size of 0.9 x 0.9 x 1.0). The functional data were acquired in an interleaved order (EPI, TR = 2 sec; 30-32 slices to cover the whole brain, FOV = 240 mm, slice thickness = 5 mm, 0 gap, 64 x 64 matrix, resulting in a voxel size of 3.75 x 3.75 x 5.0). Functional images were taken in an oblique orientation with each slice being perpendicular to the long axis of the hippocampus. We acquired two functional sessions with 190 frames each. The first three frames were dropped for signal equilibrium. The fMRI protocol also included two other experimental tasks that are not part of the current analysis.
5.3.4 Data Analysis

All pre-processing of imaging data was performed using SPM8 (Statistical Parametric Mapping 8; Wellcome Department of Imaging Neuroscience, London). Functional images were co-registered to the subject’s anatomical image, and temporally realigned and unwarped. The subject’s anatomical image was segmented and spatially normalized to the T1-weighted Montreal Neurological Institute (MNI) template and the normalization parameters were then written to the functional data. Finally, fMRI data were smoothed using a Gaussian kernel of 8 mm full width half maximum (FWHM). SPM motion parameters were inspected for outliers (motion > 2 mm in any direction) but no subjects had to be excluded from the analysis.

5.3.4.1 Spatiotemporal Partial Least Squares

A spatiotemporal Partial Least Squares (ST-PLS) analysis was conducted in order to examine the time course of hippocampal activity during AM retrieval. PLS is a multivariate, correlational technique that allows the analyses of associations between brain activity and experimental conditions without assumptions about the shape and time course of the hemodynamic response function (McIntosh, Chau et al. 2004; McIntosh and Lobaugh 2004; Krishnan, Williams et al. 2011). Therefore, ST-PLS allows the investigation of changes in event-related brain activity for each TR of a trial event. In the current analysis, we examined time windows of eight one-TR frames (i.e., lags) for all AM and math trials.

Detailed descriptions of PLS can be found elsewhere (Krishnan, Williams et al. 2011). In brief, PLS uses singular value decomposition (SVD) to extract ranked latent variables (LVs) from the covariance matrix of brain activity and conditions. These LVs express patterns of brain activity associated with each condition. When applying PLS to event-related fMRI data, patterns of brain activity are calculated for each lag, providing a time course of activity associated with the experimental conditions. Statistical significance of the LVs was assessed using permutation testing. In this procedure, each subject’s data was randomly reassigned (without replacement) to different experimental conditions, and a null distribution was derived from multiple permutated solutions. In the current experiment, we used 500 permutations and considered LV as significant if p < 0.05. Further, we assessed the reliability of each voxel that contributed to a specific LV’s activity pattern using a bootstrapped estimation of the standard error (i.e., bootstrap ratio, BSR). For each bootstrapped solution (100 in total), subjects were sampled randomly with replacement.
and a new analysis was performed. In the current study, we considered clusters of 10 or more voxels with BSRs greater than 3.00 (roughly equal to a p < 0.003) to represent reliable patterns of activation.

5.3.4.2 Seed Partial Least Squares

In order to examine whether hippocampal-neocortical interactions change between AM construction and elaboration, we conducted a seed PLS analysis. Seed PLS examines the relationship between a target region (seed voxel) and signal intensities in all other brain voxels as a function of the experimental conditions over time (Krishnan, Williams et al. 2011). The general difference to ST-PLS is that, in seed PLS, the covariance matrix used for SVD stems from correlation values between seed voxel and all other voxels for each experimental condition (i.e., rather than brain activity values per condition).

We selected a seed in the left anterior hippocampus (ant IHC, MNI: -20 -10 -22) because this region differentiated AM retrieval from the math task reliably (as indicated by its high BSR) from lag 2 onward and showed sustained activation throughout AM retrieval (see Figure 5.1, and Table 5.1 for hippocampal peak voxels). Of note, although we were interested in a possible anterior-posterior hippocampal dissociation, we chose a single seed for the seed PLS analysis in order to differentiate functional connectivity between two time points (reflecting construction and elaboration) and not between two hippocampal regions. We therefore extracted signal intensities from the same seed, the left anterior hippocampus, at an early time point (lag 2) of AM retrieval, at which participants were searching for a specific AM (construction), and a later time point (lag 6), at which participants continued recovery and mentally “replayed” episodic details of the event (elaboration). These lags were selected as they fell comfortably within the timeframes of the construction and the elaboration phases for most items and most subjects, as indicated by participants button presses (see behavioral results section). We used a non-rotated version of seed PLS which allowed us to pre-specify a contrast (as opposed to mean-centered ST-PLS, which identifies contrasts among conditions in a data-driven manner) between hippocampal functional connectivity at lag 2 and lag 6. This contrast differentiates brain regions whose activity correlates strongly with hippocampal activity at lag 2 from brain regions whose activity correlates strongly with hippocampal activity at lag 6. This pattern does not exclude the possibility that some brain regions correlate with hippocampal activity at both lag 2 and lag 6;
however, the correlation at one time point has to be stronger than at the other time point. Again, we used 500 permutations to assess significance of the LV and 100 bootstrap samples to assess reliable voxels. We considered clusters of 5 or more voxels with a BSR greater than 2.00 (roughly equal to a p value < 0.04). Of note, seed PLS calculates correlations between seed activity at pre-specified time points (here lags 2 and 6), and activity in all remaining brain voxels at each time point within a trial’s time window (here 8 lags). In our case, only voxels whose activity at lag 2 correlated with lag 2 hippocampal activity and voxels whose activity at lag 6 correlated with lag 6 hippocampal activity were meaningful to our hypothesis. We felt that this limitation justified the choice of a lower statistical threshold.

5.3.4.3 Structural Equation Modeling

While our preceding seed PLS analysis was restricted to functional connectivity from a single seed, the left anterior hippocampus, here we aimed to explicitly examine connectivity from anterior and posterior regions in the hippocampus with a specific emphasis on the different phases of AM retrieval. To do this we used structural equation modeling (SEM; LISREL 8.80, Student Edition, Scientific Software inc., Mooresville, IN) which examines interregional correlations and anatomical pathways among selected brain areas as the input to compute path coefficients (see McIntosh AR and Gonzalez-Lima F 1994 for detailed description of SEM for neuroimaging data). These path coefficients provide information about the strength and directionality of influences between two areas and can, in distinction from symmetrical correlation analysis such as seed PLS, differ between two connected regions as a function of other influences in the model (McIntosh and Protzner 2012).

5.3.4.3.1 Region Selection

Our region selection for the SEM model was based on the highest bootstrap ratios and cluster size of the seed PLS analysis as well as functional relevance to AM retrieval (Greenberg and Rubin 2003; Conway 2009). Eleven voxels from regions whose activity co-varied with the left anterior HC were included in this model (MNI coordinates in brackets): bilateral anterior HC (ant lHC = -20 -10 -22; ant rHC = 28 -8 -16 ), bilateral posterior HC (post lHC = -24 -38 -2; post rHC = 26 -38 -2), left dorsomedial prefrontal cortex (ldmPFC = -6 50 44), left ventrolateral prefrontal cortex (l vlPFC = -50 36 -10), left medial prefrontal cortex (lmPFC = -4 56 -14),
bilateral middle occipital cortices (lmidOcc = -22 -72 48; rmidOcc = 30 -76 36), left lingual gyrus (lLingual = -24 -72 2) and right fusiform gyurs (rFusiform = 22 -78 36).

5.3.4.3.2 Model Construction

An anatomical model of multi-synaptic connections between these regions was derived from known primate neuroanatomy (Suzuki and Amaral 1994; Lavenex, Suzuki et al. 2002; Kondo, Saleem et al. 2005; Fanselow and Dong 2010; Ranganath and Ritchey 2012). As we were especially interested in the role of the hippocampus during AM construction and elaboration, we only included hippocampal-neocortical connections and neglected cortico-cortical connections. We then constructed a functional model for AM retrieval during construction and elaboration. For each individual, the voxel signal intensities were extracted from each chosen region from lag 2 (construction) and lag 6 (elaboration) using the PLSgui.

5.3.4.3.3 Path Analysis

For the path analysis, the matrix of correlations between the extracted signal intensities was used to calculate path coefficients, which represent the magnitude of influence of each directional path. Using a stacked-model approach, we tested for differences in effective connectivity between AM construction and elaboration (McIntosh and Gonzalez-Lima 1994). This approach uses two models, a null and an alternative model. In the null model, path coefficients were set to be equal, whereas in the alternative model, path coefficients were free to vary. In order to test whether the null or alternative model provides a better fit to the data, we conducted a goodness-of-fit chi square test for each model. Smaller chi square values indicate better model fit. We therefore used the chi square difference test to evaluate whether the difference between both chi square values was significant. In our case, the alternative model had a significantly lower chi square value than the null model, and thus provided a better fit to the data. To determine which connections contributed to the better fit of the alternative model, individual paths were allowed to vary in a step-wise manner and chi square values were re-calculated each time. These chi square values were then evaluated against the chi square value of the null model using the chi square difference test. Connections that increased the model fit (i.e., lowered the chi square value significantly) were considered significant and were left to vary in the model. Because the order in which the connections vary could influence the results, we allowed connections to vary in four different orders (i.e., from anterior to posterior, from posterior to anterior, from the left to the
right hemisphere, and from the right to the left hemisphere). The order that resulted in the smallest remaining chi square distance (which was the model that began by anterior connections to vary) was chosen as the best fit. Models with stability indices below or equal 1 were considered sufficiently stable (Kline 2005).

5.4 Results

5.4.1 Behavioral Results

Participants indicated on average after 2.9 sec (+/- 0.7 sec) that they had an AM in mind and would begin the elaboration phase, whereas they responded on average 3.9 sec (+/- 1.1 sec) to indicate that they solved the math problem and would start adding 3’s to the solution (t(26)=2.92, p<0.01). Out of the 22 AM trials, participants rated 14 (+/- 4.4) as vivid and 16.7 (+/- 3.9) of the 22 math trials as easy (t(26)=1.72, p>0.05).

5.4.2 Early Hippocampal Activation

To examine the time course of hippocampal activity during AM retrieval, we conducted a ST-PLS. PLS identified one significant pattern, separating AM and math trials (LV 1, p<0.001). The pattern describing the AM retrieval comprised all of the core and most of the secondary AM regions identified by a meta-analysis (Svoboda, McKinnon et al. 2006). Please see Table 5.1 and Table 5.2 for a list of hippocampal peaks and other activated brain regions. Of special interest, we found that the left anterior hippocampus (MNI, -20 -10 -22) was activated one lag earlier than the right hippocampus during AM trials (see Figure 5.1). For the remaining lags, both hippocampi showed greater activation during AM than math trials, replicating previous findings of sustained hippocampal activation throughout AM retrieval (Addis, Wong et al. 2007; St Jacques, Kragel et al. 2011).
Figure 5.1 Temporal Characteristics of Hippocampal Activation during AM Retrieval

A. Hippocampal activation (slice number: y= -10) in red across 7 lags (= 14 sec) that showed a greater bootstrap ratio (BSR) than 3.0 and a cluster size of >10 contiguous voxels. Activation is displayed on a T1-weighted MRI.

B. Percent signal change for the left (lHC, MNI: -20 -10 -22; peak in lag 2) and right (rHC, MNI: 26 -16 -18; peak in lag 3) hippocampus during AM retrieval (memory) and the control task (math).

Table 5.1: Hippocampal Peak Coordinates during AM Retrieval in Healthy Controls

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Lag = time bins of 2 sec; coordinates are given in MNI space, BSR = bootstrap ratio (significance threshold: BSR > 3.0, approx. p = .003); CS = cluster size (significance threshold: CS > 10 contiguous voxels)
Table 5.2: Whole Brain Peak Coordinates during AM Retrieval in Healthy Controls

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<th>Coordinates</th>
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<td>54</td>
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<td>34</td>
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<td></td>
<td>Middle occipital gyrus</td>
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<td>-88</td>
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<tr>
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<td>-</td>
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<td></td>
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<td>-10</td>
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Lag = time bins of 2 sec; BA = approx. Brodman area; Coordinates are given in MNI space; BSR = bootstrap ratio (significance threshold: BSR > 3.0, approx. p = .003); CS = cluster size (significance threshold: CS > 10 contiguous voxels)
5.4.3 Functional Hippocampal-Neocortical Connectivity during AM Retrieval

In this analysis, we examined functional connectivity from the same region, the left anterior hippocampus, at two different time points during AM retrieval that corresponded to the construction and elaboration stages. This analysis revealed one significant pattern that separated construction and elaboration (LV 1, p = 0.03; see Figure 5.2 and Table 5.3 for all correlated brain regions). During construction, activation of the left anterior hippocampus was correlated with a small set of brain regions (in total 2313 voxels), including the right anterior hippocampus and mainly left fronto-temporal regions. During elaboration, widespread brain activation (in total 26683 voxels) correlated with activity in the left anterior hippocampus. These regions included visual-perception cortices, auditory association cortices and motor cortices. Of note, we did not see this same pattern in a direct univariate contrast of mean activity (rather than connectivity) of early/construction versus late/elaboration phases (see Figure 5.3).

This analysis shows that the same hippocampal region communicates with different cortical regions during construction and elaboration. We then used effective connectivity to determine whether the directionality of hippocampal-neocortical interactions differs during the two phases.
Figure 5.2: Functional Hippocampal-Neocortical Networks during AM Retrieval

Functional connectivity between the hippocampal seed (IHC, MNI: -20 -10 -22) and other brain regions during construction (= lag 2) and elaboration (= lag 6) displayed on a rendered T1-weighted MRI. BSR >2.0 and clusters of more than 5 contiguous voxels were considered significant.
Figure 5.3: Mean-Based Contrast between Construction and Elaboration of AM Retrieval

Mean-based contrast between construction and elaboration of AM retrieval. Construction is defined as TR1&2 and elaboration as TR4&5. Activation map is overlaid on a T1-weighted MRI. Colorbars display T-statistics. The mean-based contrast between both AM stages does not reveal the same pattern as the connectivity-based analysis.

Table 5.3: Functional Hippocampal-Neocortical Connectivity during AM Retrieval

<table>
<thead>
<tr>
<th>Lag 2: Construction</th>
<th>Hemisphere</th>
<th>BA</th>
<th>Coordinates</th>
<th>BSR</th>
<th>CS</th>
<th>SEM</th>
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<td>Y</td>
<td>Z</td>
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<td>66</td>
<td>-54</td>
<td>24</td>
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<td>Region</td>
<td>Side</td>
<td>Coordinates</td>
<td>F-value</td>
<td>BSR</td>
<td>Cluster Size</td>
<td>Significance</td>
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<td>--------------------------------</td>
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**Lag 6: Elaboration**

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<th>Significance</th>
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<td>-2.55</td>
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*BA = approx. Brodman area; Coordinates are given in MNI space; BSR = bootstrap ratio (significance threshold for a. construction: BSR > 2.0, approx. p = .04; and b. elaboration: BSR < -2.0, approx. p = .04); CS = cluster size (significance threshold: CS > 10 contiguous voxels); * = voxels included in the SEM analysis*
5.4.4 Directed Hippocampal-Neocortical Connectivity during AM Retrieval

One of our main research goals was to assess the role of the hippocampus as a central hub within the AM network. Further, we aimed to assess interactions between the anterior and posterior hippocampus and the rest of the AM retrieval network during construction and elaboration, respectively. We therefore built a model of the AM retrieval network based on brain regions found to be involved in construction or elaboration in our PLS analysis (see Figure 5.4 for all regions included in the SEM analysis and their correlation values to the hippocampal seed), which included the anterior and posterior hippocampi bilaterally, and we examined the directionality of these connections during each AM retrieval phase.

**Figure 5.4: Location of SEM Nodes and Relation to the Seed**

In addition to the seed voxel in the ant IHC, 10 regions were included in the following SEM analysis. For clarity, individual clusters are displayed separately on a T1-weighted MRI. The functional connectivity (correlation coefficient, r) between the seed and the peak voxel of the cluster during construction (Con; lag 2) and elaboration (Ela; lag 6) is shown underneath each region.
Figure 5.5: Effective Hippocampal-Neocortical Networks during AM Retrieval in Healthy Controls

Red arrows represent positive (solid) or negative (dashed) effective connections that differed between construction and elaboration, white arrows represent anatomical connections that were included in the model but did not differ between both AM retrieval processes. The thickness of the arrows indicates the strength of the influence from one region to the other (path coefficient).

We found that the model in which path coefficients were free to vary was a better fit to our data than the model in which path coefficients were fixed (CHIdiff=44.72, df=22, p=0.003, all stability indices ≤1), indicating that effective connectivity differed significantly between construction and elaboration (see Figure 5.5). We found six connections that differed between the two AM phases (path coefficients in brackets): During construction, the left anterior hippocampus had a greater positive influence on the dmPFC (ant lHC to ldmPFC, construction: 0.7, elaboration: 0.06) and the right anterior hippocampus (ant lHC to ant rHC, construction: 0.6, elaboration: 0.35) than during elaboration. Further, both left and right anterior hippocampi had a positive influence on activity in the posterior part of the hippocampi, while this influence was
slightly negative during elaboration (ant IHC to post IHC, construction: 0.12, elaboration: -0.1; ant rHC to post rHC construction: 0.21, elaboration: -0.02).

During elaboration, the left posterior hippocampus had a greater influence on the left middle occipital gyrus (post IHC to lmidOcc, construction: 0.05, elaboration: 0.49), while the right posterior hippocampus a greater influence on the right fusiform gyrus than during construction (post rHC to rFusiform, construction: -0.02, elaboration: 0.29). These findings indicate key roles for both hippocampi in the directed mediation of hippocampal-neocortical interactions during AM retrieval that shift from a hippocampal-frontal network at construction to a hippocampal-temporo-occipital network at elaboration.

5.5 Discussion

We report that the hippocampus is critically involved in coordinating different networks for constructing and elaborating autobiographical memories. Using multivariate connectivity analyses, our data provide direct and compelling experimental evidence that construction is supported by a fronto-temporal network and elaboration by a widespread temporo-parieto-occipital network and further that these networks interact with anterior and posterior hippocampal regions, respectively. Importantly, these networks were not readily identified by voxel-based analyses, indicating that network approaches are particularly suited to revealing interactions amongst regions involved in complex cognitive processes such as autobiographical retrieval. Recently, St Jacques and colleagues (2011) used another multivariate technique, ICA, and extracted four different functional networks underlying AM construction and elaboration, including an MTL, medial PFC, frontoparietal, and cingulooperculum network. Although they did not impose a specific contrast between networks supporting construction and elaboration, they found that the frontoparietal and cingulooperculum networks peaked during construction and declined during elaboration whereas the MTL and medial PFC networks showed sustained activation throughout the AM retrieval. Thus, our findings are complementary and we show additionally those hippocampal-neocortical networks (identified by direct contrast) that are uniquely associated with elaboration.
5.5.1 AM Construction: Hippocampal-Fronto-Temporal Connectivity

As Conway predicted more than 10 years ago (Conway and Pleydell-Pearce 2000), we found that AM construction was supported by a small network comprising the left hippocampus and mainly fronto-temporal cortices, including both medial and lateral regions of the frontal and temporal lobes. Our results are in agreement with other neuroimaging studies showing fronto-temporal involvement during AM construction (Daselaar, Rice et al. 2008; Holland, Addis et al. 2011; St Jacques, Kragel et al. 2011; Rabin and Rosenbaum 2012). However, we expand this knowledge by showing that these regions form a transient network linked to the left anterior hippocampus and furthermore that the left anterior hippocampus effectively influences activity in the dmPFC during AM construction. Although the dmPFC has been shown to be a consistent part of both the network engaged during AM retrieval (Svoboda, McKinnon et al. 2006) and the resting state default mode network (Buckner, Andrews-Hanna et al. 2008), several studies have shown it can segregate from the hippocampal network in both settings (Andrews-Hanna, Reidler et al. 2010; St Jacques, Kragel et al. 2011). Nonetheless, we show here that the hippocampus can form transient links to this brain region during specific task circumstances. While the specific contribution of the dmPFC to autobiographical retrieval is unclear, it has been shown to be engaged in self-guided retrieval of semantic information (Binder, Desai et al. 2009), which is consistent with Conway’s idea of AM construction. Of interest, our SEM finding that hippocampal activation influences the activation pattern in dmPFC, rather than the reverse, is new and interesting as it suggests a strong ‘bottom-up’ direction of influence in construction versus elaboration. However, it might be that this direction of influence holds true only for readily accessible AMs. Using a similar effective connectivity analysis (dynamic causal modelling), St Jacques et al. (2011) showed that the MTL influenced the PFC during AM construction only in cases where the AM was retrieved quickly but not for AMs that were brought to mind more effortful. The relatively short mean retrieval time of our participants (our study: 2.9 +/- 0.7 sec, St Jacques et al.: 6.5 +/- 2.11 sec) indicates that the AMs in our study were also easily accessible which might have contributed to this result.

In contrast, the engagement of medial parts of the prefrontal cortex has been attributed to self-referential processes (Howe and Courage 1997; Conway and Pleydell-Pearce 2000). It is therefore not surprising that in our data functional and effective connectivity between the
hippocampus and mPFC did not differentiate between construction and elaboration, since both processes rely on self-referential information (Svoboda, McKinnon et al. 2006).

5.5.2 AM Elaboration: Hippocampal-Temporo-Parieto-Occipital Connectivity

Again, as Conway predicted, we found that AM elaboration was supported by a wide-spread network comprising the bilateral anterior and posterior regions of the hippocampi, as well as temporal, parietal and occipital cortices (Conway and Pleydell-Pearce 2000). Strikingly, our effective connectivity analysis revealed that both posterior hippocampi actively influenced activity in visual-perceptual areas. Whereas the retrieval of visual, emotional and auditory information is considered a crucial part of vivid AM elaboration and should be supported by a wide-spread network comprising most primary and associative cortices (Greenberg and Rubin 2003; Svoboda, McKinnon et al. 2006; Conway 2009), there is surprisingly little experimental evidence that such regions actually contribute to AM elaboration. In fact, the majority of studies that examined the spatio-temporal characteristics of AM retrieval did not observe wide-spread activation in visual-perceptual areas during elaboration (Addis, McIntosh et al. 2004; Addis, Wong et al. 2007; Holland, Addis et al. 2011; Rabin and Rosenbaum 2012). Only one study reported greater activation in visual cortices during elaboration than construction (Daselaar, Rice et al. 2008) but even this study did not show the wide-spread posterior activation predicted by various AM theories (Brewer 1986; Conway and Pleydell-Pearce 2000; Greenberg and Rubin 2003; Conway 2009). A reason for this discrepancy might be that the above-mentioned studies used mean-based activation to extract differences between either AM construction and elaboration, or AM retrieval and some control task (see St Jacques PL et al. 2011 for an exception). We reason that we were able to reveal the full extent of the elaboration network by using connectivity rather than mean-based measurements. That is, typical task-based analyses using t-tests focus solely on whether the mean activation in a given brain region differs between two experimental conditions, while connectivity analyses evaluate how two brain regions covary in different experimental conditions. In fact, it is entirely possible that the experimentally induced difference in regional mean activity (i.e., main effects) is not significant, but that the change in the relationship between two regions due to experimental manipulation (i.e., interaction effect) assessed by connectivity analyses is significant. This finding would be missed if the covariance of the two brain regions was not evaluated (McIntosh and Gonzalez-Lima...
1994). Our data support this notion, in that a direct contrast between AM construction and elaboration that was based on mean activation showed very little specific engagement of posterior regions during elaboration, whereas the covariance-based seed PLS revealed a widespread elaboration network. Although St Jacques et al (2011) also used a covariance based method, ICA, they did not find a posterior network that peaked during elaboration. One potential reason for this discrepancy is that we specified a direct contrast in our non-rotated seed PLS between hippocampal connectivity during construction versus elaboration. This aspect forced the analysis to assess differences between the two conditions which may have been missed by a data-driven ICA analysis.

5.5.3 The Role of the Hippocampus in AM Retrieval

The functional importance of the hippocampus in AM retrieval, and generally contextually-rich episodic memory retrieval, is well established (Svoboda, McKinnon et al. 2006; Ranganath 2010). Consistent with other studies, we found sustained hippocampal activation throughout AM retrieval trials (Addis DR et al 2007; St Jacques PL et al 2011; but see Daselaar SM et al 2008). However, in this paper, we extend beyond previous findings by demonstrating how the hippocampus plays a crucial role in coordinating the construction and elaboration networks. Although other studies have shown that the hippocampus can form parts of different memory networks during encoding versus retrieval (McCormick, Moscovitch et al. 2010), and during episodic versus semantic retrieval (Rajah and McIntosh 2005), to our knowledge this is the first demonstration of the hippocampus connecting with separate sets of brain regions during different stages of the same AM trials.

Further, in our data, the left anterior hippocampus was functionally connected to the right anterior hippocampus during construction and to bilateral posterior hippocampi during elaboration. Whereas involvement of the anterior hippocampus has been attributed to access of specific AMs and gist-like episodic memories, involvement of the posterior hippocampus has been linked to recollection, memory for complex scenes and spatial navigation (Poppenk and Moscovitch 2011; Viard, Desgranges et al. 2012). For example, Poppenk (2013) proposes that in AM retrieval the role of the anterior hippocampus might be to link together principal actors, actions and general settings, and the role of the posterior hippocampus might be to retrieve the exact spatio-temporal context and episodic details of an event. Although these theories
emphasize the anatomical and functional dissociation between anterior and posterior parts of the hippocampus, there are major anatomical and functional connections between these segments which might facilitate integration of different information (Patel, Fujisawa et al. 2012; Sloviter and Lomo 2012). For example, Sloviter (2012) reviews that the longitudinal associational axon projections of the mossy fibres in the dentate gyrus of the rat spans around 6.6mm (roughly 80% of the total length of the rat hippocampus). Further, a recent lesion study in rats pointed towards the intermediate hippocampus as an important site for the integration of behavioral-control processes (i.e., associated with anterior hippocampal function) and place codes (i.e., associated with posterior hippocampal function, Bast T et al. 2009). Our SEM results revealed that both anterior segments positively influenced posterior segments of the hippocampi during construction to a greater extent than during elaboration. In our experiment, AMs were brought voluntarily to mind using event cues. We therefore speculate that during construction, gist-like information indexed by the anterior part of the hippocampus might have initiated the search for visual-perceptual information indexed by the posterior hippocampus during elaboration. In sum, our data support the functional dissociation of anterior and posterior segments of the hippocampus but also emphasize its functional integration in vivid AM retrieval.

5.6 Limitations and Future Directions

A limitation of our study is the lack of information on the remoteness of the individual AMs, especially in the context of the wide age range of our participants. The debate of hippocampal involvement in remote memory has been addressed by various studies and the evidence so far indicates that the hippocampus remains involved in remote AMs, as long as they remain vivid and detail-rich (Addis, Moscovitch et al. 2004; Moscovitch, Rosenbaum et al. 2005; Sheldon and Levine 2013). In the current study, most of the AMs were reported as vivid. We therefore expect that our results are more likely to have been influenced by the vivid memories rather than the faint ones. Of note, we are currently exploring these issues in a separate paper by comparing AM construction and elaboration networks of healthy controls to patients with medial temporal lobe damage who are known to be impaired in retrieval of vivid AMs (St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011).
Further, we would like to acknowledge that our effective connectivity results represent a “working model”, recognizing the truth of the assertion that essentially all models are wrong but some are useful (Box and Draper, 1987). Decisions about regions to include and how they are connected had to be made and thus including other neocortical regions or neocortico-cortical connections might have yielded different results. However, we believe that examining patterns and directions of connectivity will help to both elaborate and constrain biologically plausible models and to generate new hypotheses about the nature of how brain regions interact during complex cognitive tasks.

5.7 Conclusions

As initially proposed by Conway, we found evidence that AM construction and elaboration are supported by different sets of brain regions. We add that the hippocampus plays a key role in coordinating these flexible, transient neocortical networks during AM retrieval. Further, our data revealed a novel and interesting intrahippocampal dialogue between different stages of AM retrieval. We were able to illustrate this complex network interplay with the use of functional and effective connectivity analyses that assess the relationship between brain areas instead of local mean activation levels. These findings support the idea that in order to understand the full function of a brain region it is important to examine its neuronal context, i.e., what other regions it interacts with under different experimental conditions (McIntosh 2000).
6 Connectivity Changes during Construction and Elaboration of Autobiographical Memories in Patients with Medial Temporal Lobe Epilepsy
6.1 Introduction

The goal of the current study is to assess how the flexible interplay between hippocampus and neocortex during construction and elaboration of AMs is affected by damage to the MTL. A general theme of this thesis is the differentiation between stable functional connectivity patterns, seen for example within the DMN, if sampled over an extended period of time (see chapter 0 and 0), and the flexible functional dynamics that support individual tasks, such as the construction and elaboration of AMs (see chapter 0). As described in the previous chapter, in healthy controls the left hippocampus appears to be an important hub not only to support vivid, detail rich AM retrieval in general, but also to support the flexible change of functional connectivity patterns underlying the two AM phases, construction and elaboration. The aim of the last study of this thesis is to examine how MTL damage affects this dynamic hippocampal-neocortical dialogue.

Few other studies have examined general AM retrieval in patients with mTLE. While unilateral mTLE typically does not lead to global AM amnesia (but see for a description of transient epileptic amnesia in mTLE (Butler, Graham et al. 2007; Milton, Butler et al. 2012)), there are clear differences in the quality of AMs described by patients with mTLE and healthy controls (Viskontas, McAndrews et al. 2000; Voltzenlogel, Despres et al. 2006; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011). For example, patients with mTLE have little difficulty recalling the general story line or gist of an AM but are impaired in recalling specific episodic elements of an AM. Remarkably, this deficit extends even to the most remote time periods of early childhood, even long before seizure onset in many patients (Viskontas, McAndrews et al. 2000). Further, patients with mTLE can accurately recite the overall temporal order of AMs but are impaired in reciting the minute-to-minute evolution of events (St-Laurent, Moscovitch et al. 2011). In agreement with this proposal are data showing that a patient with severe bilateral MTL damage could provide the overall layout of his highly familiar neighbourhood but was unable to retrieve any specific details about this familiar area of his home city (Rosenbaum, Kohler et al. 2005). Together, these studies suggest that patients with mTLE can construct the general organization of an AM, or in Conway’s terms, they do not lack the general hierarchical self-knowledge structure (Conway and Pleydell-Pearce 2000; Conway
2009), however, they seem to be unable to retrieve the episodic elements embedded in this organizational structure in the same way that healthy controls commonly do in the elaboration phase of AM retrieval.

While no study up to today examined differences in construction and elaboration in patients with mTLE, fMRI studies examining differences in AM retrieval between patients with mTLE and healthy controls generally show a reduction in brain activity not only within the damaged MTL but across all regions typically activated during AM retrieval, including most regions of the DMN (Addis, Moscovitch et al. 2007; McAndrews and Cohn 2012; St-Laurent 2012). Interestingly, also areas sensitive to perceptual richness showed less activation in patients with mTLE than healthy controls during AM retrieval, further suggesting a deficit especially in the elaboration phase of AM (St-Laurent 2012). Additionally, examining effective connectivity during the recall of pre-selected AMs, patients with left mTLE differed from healthy controls in that they did not rely on a hippocampal-centric AM network, but instead on increased connectivity between posterior retrosplenial cortex and anterior prefrontal cortex (Addis, Moscovitch et al. 2007). While this finding does not speak to the different stages of AM retrieval specifically, one might assume that this paradigm taps more into the elaboration phase since AMs were pre-selected and reminder cues presented shortly before scanning. Thus, these findings suggest that patients with mTLE might rely on a different neuronal network to elaborate on impoverished AMs. In fact, the elaboration of these AMs might differ in terms of both behavior and neuronal underpinnings from this process in healthy controls.

There are no studies yet available that examined construction and elaboration processes separately in patients with mTLE. However, the findings reviewed above suggest that the hippocampus in mTLE might not have the capability to switch flexibly between networks supporting different stages of AM retrieval. From this perspective it is interesting to turn to computational models which suggest that signal complexity or entropy provides important information on the tissue’s capability to form transient network constellations and respond to current task demands (McIntosh, Kovacevic et al. 2010; Misic, Mills et al. 2010; Deco, Jirsa et al. 2011). Therefore, a reasonable expectation would be that the damaged MTL has reduced complexity or entropy. Indeed, using iEEG, Protzner et al. (2010) could show that the damaged hippocampus has less entropy than the contralateral, unaffected hippocampus. Extending these findings to fMRI, our group could further show that the variability of BOLD signal acquired
during AM retrieval explained episodic memory capacity in mTLE patients (Protzner, Kovacevic et al. 2013). These findings are in line with the current proposal that the affected hippocampus might not be able to support the critical switch between construction and elaboration networks underlying vivid, detail-rich AM retrieval.

In sum, construction and elaboration of vivid AM recall in the healthy brain is supported by different transient hippocampal-neocortical networks. Our findings with healthy controls (see chapter 5) implicate the hippocampus as the major hub of transient neocortical networks that support this rich functional repertoire underlying the recall of unique vivid, detail rich AMs. Consequently, damage to the hippocampus leads to a reduction in its capability to form and support this functional repertoire, leading in turn to impoverished AM retrieval that might be mostly supported by communication between neocortical regions. Therefore, the current study addresses the hypothesis that functional connectivity of the hippocampi is more stable across AM retrieval in mTLE than in healthy controls.

### 6.2 Methods

#### 6.2.1 Participants

We included 12 patients with L-mTLE and 12 age and education matched healthy controls in this study who gave written informed consent in accordance with a research protocol approved by the University Health Network Ethics Board (see Table 6.1).

#### 6.2.2 Experimental Procedure

The task and scanning parameters were identical to those reported in Chapter 5.3. In short, prior to scanning, the task was explained and an exemplary recall of a vivid AM was illustrated to the participants. Participants were then asked to complete 6 trials of each condition and the experimenter probed the contents of all retrieved AMs to confirm that the participants understood the instructions, such that the generated AM events were specific in time and place.
Extra care was given to ensure that patients with mTLE understood the task properly by providing additional examples of AM construction and elaboration.

The task consisted of two conditions, 22 AM retrieval and 22 math trials which were presented randomly during scanning. During the AM retrieval condition, an event cue was presented on the screen, for example “Party” and the participants were asked to recall a specific party of their personal past. Once they had one particular event in mind, they were asked to press a button that would signal the end of AM construction and the beginning of the AM elaboration, in which participants were asked to retrieve as many episodic elements as possible to that AM. In the math condition, participants were asked to solve a simple math problem, press a button when they had the solution in mind and add 3’s to the solution for the rest of the trial duration. At the end of each trial, participants were asked to rate the AM retrieval as either vivid or faint and the math solving as difficult or easy (see (Addis, Wong et al. 2007) for a similar design).

### Table 6.1: Demographical and Clinical Information (Study 4)

<table>
<thead>
<tr>
<th></th>
<th>Left mTLE (n=12)</th>
<th>Controls (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>(n=12)</td>
<td>(n=12)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/6</td>
<td>8/4</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>11/1</td>
<td>10/2</td>
</tr>
<tr>
<td>Age at scan, mean (SD)</td>
<td>39.6 (11.4)</td>
<td>39.9 (13.1)</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
<td>15.2 (2.7)</td>
<td>15.4 (5.2)</td>
</tr>
</tbody>
</table>

**Clinical parameters**
- MTS (yes/no) 7/5 n.a.
- Other MRI lesions (yes/no)* 2/10
- Age of onset, mean (SD) 20.3 (15.9) n.a.
- Epilepsy duration 20.9 (17.8) n.a.

MTS= Medial temporal lobe sclerosis
*One patient had a single heterotopion in the left occipital lobe, and another patient had a left temporal dysembryoplastic neuroepithelial tumor (DNET)
6.2.3 Data Acquisition

The fMRI data were acquired and preprocessed identical to the data of the healthy controls in the previous chapter. Please see Chapter 5.3.3 for more details.

6.2.4 Data Analysis

6.2.4.1 Univariate Analyses

We first examined BOLD signal changes during AM retrieval in both healthy controls and patients with left mTLE using univariate contrasts between the AM retrieval and math condition. Both conditions were modeled as mini blocks of 8 TR duration. For contrasts, each participant’s data were analysed as a fixed-effects model and the resulting contrast images were taken to the second level and analysed as a random-effects one sample t-test in SPM8. On a whole brain level, we considered voxel cluster extending 20 adjacent voxels and the peak p value less than 0.001 as significant. Using a two sample t-test on the same contrast images, we then compared healthy participants and patients with L-mTLE. Here, we considered voxel cluster extending 20 adjacent voxels and the peak p value less than 0.005 as significant.

6.2.4.2 Functional Connectivity Cross-Correlations

In a next step, we aimed to examine whether hippocampal functional connectivity would support the dynamic change between AM construction and elaboration. Here, we used the model derived from healthy controls showing flexible changes in effective connectivity between both anterior and posterior hippocampi and neocortex. This model contained the same 11 regions of interest as in the model derived from healthy controls (see Figure 5.4, MNI coordinates in brackets): bilateral anterior HC (ant lHC = -20 -10 -22; ant rHC = 28 -8 -16), bilateral posterior HC (post lHC = -24 -38 -2; post rHC = 26 -38 -2), left dorsomedial prefrontal cortex (ldmPFC = -6 50 44), left ventrolateral prefrontal cortex (lvlPFC = -50 36 -10), left medial prefrontal cortex (lmPFC = -4 56 -14), bilateral middle occipital cortices (lmidOcc = -22 -72 48; rmidOcc = 30 -76 36), left lingual gyrus (lLingual = -24 -72 2) and right fusiform gyurs (rFusiform = 22 -78 36). For the current study, we extracted signal intensities from all participants for each region in the model for the early (lag 2) and late (lag 6) time point. We then calculated correlations coefficients, indicating functional connectivity, for all connections that were in the original model. As a measure of the dynamic change in connectivity between both AM retrieval stages, we calculated
the absolute difference in functional connectivity between the entire set of connections in the model for healthy controls and patients with left mTLE. Further, as our hypothesis was primarily that hippocampal connectivity would be less flexible in patients with left mTLE than healthy controls, we also calculated the absolute difference in connectivity for intra- and interhippocampal connections only of the construction and elaboration models for healthy controls and patients with mTLE separately. This difference reflects the degree to which functional connectivity changes between construction and elaboration. We then compared the difference in functional connectivity between patients with L-mTLE and healthy controls using the nonparametric version of a t-test, Mann-Whitney tests and considered a p<0.05 significant.

6.3 Results

6.3.1 Univariate contrasts

6.3.1.1 AM Retrieval in Healthy Controls

As previously shown, we found that healthy controls activated the entire primary and most of the secondary brain regions associated with AM retrieval to a greater extent in the AM retrieval condition than the math condition (see Figure 6.1 and Table 6.2). These regions included bilateral hippocampal and parahippocampal gyrus, bilateral lateral parietal cortices, bilateral lateral temporal cortices, PCC/Retrosplenial cortex, and medial prefrontal cortex.

![Activated Brain Regions during AM Retrieval in Healthy Controls](image)

Figure 6.1: Activated Brain Regions during AM Retrieval in Healthy Controls
This figure displays brain regions activated more during AM retrieval than math solving superimposed on a T1-weighted MRI. P<0.001, uncorrected (Cluster extent >20).
Table 6.2: Peak Coordinates of Activated Brain Regions during AM Retrieval in Healthy Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular gyrus</td>
<td>left</td>
<td>39</td>
<td>-48 -68 32</td>
<td>10.87</td>
</tr>
<tr>
<td>Inferior lateral frontal gyrus</td>
<td>left</td>
<td>47</td>
<td>-38 32 -12</td>
<td>10</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>left</td>
<td>31</td>
<td>-28 -26 -14</td>
<td>9.82</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>left</td>
<td>31</td>
<td>-6 -52 32</td>
<td>9.17</td>
</tr>
<tr>
<td>Superior medial frontal gyrus</td>
<td>left</td>
<td>9</td>
<td>-2 52 34</td>
<td>10.68</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>right</td>
<td>39</td>
<td>52 -62 24</td>
<td>9.43</td>
</tr>
<tr>
<td>Inferior medial frontal gyrus</td>
<td>left</td>
<td>32</td>
<td>-2 52 -4</td>
<td>8.49</td>
</tr>
<tr>
<td>Superior temporal pole</td>
<td>right</td>
<td>38</td>
<td>58 14 -20</td>
<td>7.42</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>right</td>
<td>26</td>
<td>-20 -16</td>
<td>7.41</td>
</tr>
<tr>
<td>Inferior lateral frontal gyrus</td>
<td>right</td>
<td>47</td>
<td>46 32 -20</td>
<td>7.3</td>
</tr>
<tr>
<td>Retrospenial cortex</td>
<td>left</td>
<td>29</td>
<td>-6 -48 10</td>
<td>7</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>right</td>
<td>24</td>
<td>-78 -34</td>
<td>6.51</td>
</tr>
<tr>
<td>Precentral</td>
<td>right</td>
<td>4</td>
<td>30 -16 68</td>
<td>6.32</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>left</td>
<td>-8</td>
<td>-54 -46</td>
<td>5.15</td>
</tr>
<tr>
<td>Precentral</td>
<td>right</td>
<td>4</td>
<td>-30 -20 74</td>
<td>5.06</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>right</td>
<td>21</td>
<td>70 -38 2</td>
<td>5.02</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>left</td>
<td>20</td>
<td>-24 -76 -12</td>
<td>4.48</td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>left</td>
<td>19</td>
<td>-20 -86 -16</td>
<td>4.18</td>
</tr>
<tr>
<td>Superior medial frontal gyrus</td>
<td>left</td>
<td>10</td>
<td>-30 64 -6</td>
<td>4.46</td>
</tr>
<tr>
<td>Inferior medial frontal gyrus</td>
<td>left</td>
<td>11</td>
<td>-2 18 -20</td>
<td>76</td>
</tr>
</tbody>
</table>

BA = approximate Brodmann Area

6.3.1.2 AM Retrieval in Patients with Left mTLE

We found that patients with left mTLE did not show any MTL activation in either hemisphere (see Figure 6.2 and Table 6.3). Other than these regions, all remaining primary and most of the secondary brain regions associated with AM retrieval were also activated more during AM retrieval than during math solving. These regions included bilateral lateral parietal cortices, bilateral lateral temporal cortices, PCC/Retrospenial cortex, and medial prefrontal cortex.
Figure 6.2: Activated Brain Regions during AM Retrieval in Patients with Left mTLE

This figure displays brain regions activated more during AM retrieval than math solving superimposed on a T1-weighted MRI. P<0.001, uncorrected (Cluster extent >20).

Table 6.3: Peak Coordinates of Activated Brain Regions during AM Retrieval in Patients with Left mTLE

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle temporal gyrus</td>
<td>left</td>
<td>21</td>
<td>-60</td>
<td>-8</td>
</tr>
<tr>
<td>Superior medial frontal gyrus</td>
<td>left</td>
<td>9</td>
<td>-2</td>
<td>52</td>
</tr>
<tr>
<td>Cuneus</td>
<td>left</td>
<td>18</td>
<td>-6</td>
<td>-94</td>
</tr>
<tr>
<td>Cuneus</td>
<td>right</td>
<td>18</td>
<td>10</td>
<td>-84</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>left</td>
<td>39</td>
<td>-46</td>
<td>-66</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>right</td>
<td>39</td>
<td>56</td>
<td>-62</td>
</tr>
<tr>
<td>Inferior temporal pole</td>
<td>right</td>
<td>21</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>right</td>
<td>21</td>
<td>58</td>
<td>-14</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>left</td>
<td>31</td>
<td>-2</td>
<td>-46</td>
</tr>
<tr>
<td>Inferior lateral frontal gyrus</td>
<td>left</td>
<td>47</td>
<td>-50</td>
<td>26</td>
</tr>
<tr>
<td>Middle lateral frontal gyrus</td>
<td>left</td>
<td>8</td>
<td>-32</td>
<td>14</td>
</tr>
<tr>
<td>Precentral</td>
<td>right</td>
<td>4</td>
<td>48</td>
<td>-20</td>
</tr>
<tr>
<td>Inferior lateral frontal gyrus</td>
<td>right</td>
<td>47</td>
<td>54</td>
<td>30</td>
</tr>
<tr>
<td>Inferior temporal pole</td>
<td>left</td>
<td>21</td>
<td>-52</td>
<td>10</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>left</td>
<td>20</td>
<td>-30</td>
<td>-40</td>
</tr>
</tbody>
</table>

BA = approximate Brodmann Area
6.3.1.3 Contrast between AM Retrieval in Healthy Controls and Patients with Left mTLE

As expected, we found that healthy controls showed greater activation of the left hippocampus during AM retrieval in comparison to patients with left mTLE (see Figure 6.3 and Table 6.4). Although patients with left mTLE did not show greater right hippocampal activation during the AM retrieval than the math condition, the difference in activation between healthy controls and patients with left mTLE did not reach significance for the right hippocampus. Interestingly however, we found that patients with left mTLE showed greater activation in right prefrontal cortices, including the dorso- and ventromedial segments and the lateral temporal cortices, including the right temporal pole and the left superior temporal segments.

**Controls > Left mTLE**

![Brain Imaging](image)

**Left mTLE > Controls**

![Brain Imaging](image)

**Figure 6.3: Difference in Brain Activation during AM Retrieval in Healthy Controls and Patients with Left mTLE**

This figure displays the contrast (AM>math) between healthy controls and patients with left mTLE. Activation maps are superimposed on a T1-weigthed MRI. P<0.005, uncorrected (Cluster extent >20).
Table 6.4: Peak Coordinates of Differences in Brain Activation during AM Retrieval in Healthy Controls and Patients with Left mTLE

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>Controls &gt; Patients with left mTLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>left</td>
<td>-34</td>
<td>-24</td>
<td>-14</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>right</td>
<td>24</td>
<td>-46</td>
<td>-42</td>
</tr>
<tr>
<td>Patients with left mTLE &gt; Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior medial frontal gyrus</td>
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<td>16</td>
<td>54</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>right</td>
<td>10</td>
<td>24</td>
<td>46</td>
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<td>11</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
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<td>-38</td>
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<tr>
<td>Inferior temporal gyrus</td>
<td>right</td>
<td>21</td>
<td>44</td>
<td>8</td>
</tr>
</tbody>
</table>

BA = approximate Brodmann Area

6.3.2 Dynamical Functional Hippocampal-Neocortical Connectivity

In a next step, we aimed to examine whether there were any changes in hippocampal-neocortical functional connectivity within a network known to support both AM phases in healthy controls (see Figure 6.4). We found that whereas controls showed mostly positive functional connectivity throughout this network at both construction and elaboration, patients with L-mTLE displayed more negative correlations at both phases (construction, CTL: 1, L-mTLE: 5; elaboration, CTL: 1, L-mTLE 4 negative correlations).

We then examined whether functional connectivity within this network would be more stable across both AM phases in patients with mTLE. We therefore calculated the difference between functional connectivity strength during construction and elaboration as a measure of the capacity to adjust connectivity strength according to changing cognitive demands. As shown in Figure 6.4, we found that the difference between functional connectivity of the overall network did not differ between patients with L-mTLE and healthy controls (Mann-Whitney test, p = 0.39). Interestingly, functional connectivity within and between both hippocampi fluctuated dramatically in healthy controls. For example, the greatest fluctuation was observed in the connection between post rHC and post lHC, in that connectivity was negligible during construction (r=0.06) and strongly positive during elaboration (r=0.76). However, this dynamic change was not seen in patients. Here the greatest fluctuation was observed in the connection...
between ant rHC and post rHC being strong during construction (r=0.73) and lower during elaboration (r=0.47). Indeed, significance testing revealed that intra- and interhippocampal connectivity changes from one AM stage to the other was significantly greater in healthy controls (Mann-Whitney test, p = 0.028). Although the range of left hippocampal activation level was slightly smaller in patients with left mTLE, this effect cannot be attributed merely to a dysfunctional activation level (see Error! Reference source not found.).

Figure 6.4: Hippocampal-Neocortical Networks during AM Retrieval in Healthy Controls and Patients with Left mTLE

Functional connectivity strengths are displayed between nodes of the AM retrieval network used in study 3 (see Figure 5.4 and Figure 5.5) for AM construction and elaboration in healthy controls (A) and patients with left mTLE (B). The thickness of the line indicates connectivity strength. Red = positive, blue = negative correlation.

The bargraphs show the differences between functional connectivity strengths during AM construction and elaboration for the entire AM network (C) and inter-/intrahippocampal connections (D) for healthy controls and patients with left mTLE. * indicates p<0.05. Of note, inter- and intrahippocampal connectivity varies between AM construction and elaboration in healthy controls but not in patients with left mTLE.
Figure 6.5: Functional Connectivity between anterior left and right hippocampus in controls and patients with L-mTLE

Illustration of correlations underlying functional connectivity between anterior left and right hippocampus. The upper panel illustrates antlHC-antrHC connectivity during construction (left) and elaboration (right) in patients with L-mTLE and the lower panel illustrates antlHC-antrHC connectivity during construction (left) and elaboration (right) in healthy controls. Note that the range of antlHC activation in patients with L-mTLE is smaller than in healthy controls but that the range is greater in the antrHC. Further, whereas controls show strong functional connectivity during construction but not elaboration, antlHC-antrHC connectivity does not differ between AM construction and elaboration in patients with L-mTLE.
6.4 Discussion

Our data suggest that the hippocampus is critically involved in coordinating transient networks for constructing and elaborating AMs because this hippocampal-neocortical interplay is disrupted in patients with mTLE. Specifically, intra- and interhippocampal functional connectivity assumed different network constellations according to the current cognitive demands in healthy controls. That is, healthy controls showed strong positive interactions between both anterior hippocampi during AM construction and strong positive interactions between both posterior hippocampi and between the anterior and posterior segment of the left hippocampus during elaboration. However, in patients who have damage to the left MTL, these fluctuations were markedly reduced, showing more similar intra- and inter-hippocampal interactions during both construction and elaboration of AMs. These findings suggest that even unilateral damage to the MTL inhibits the flexible transfer between neuronal networks that support AM construction and elaboration that relies on both MTLs in healthy controls. Our data support new computational and empirical research indicating that the exploration of different transient network configurations might be an important parameter of functional integrity of neuronal systems (Honey, Kotter et al. 2007; Ghosh, Rho et al. 2008; Garrett, Kovacevic et al. 2010; McIntosh, Kovacevic et al. 2010; Misic, Mills et al. 2010; Deco, Jirsa et al. 2011). This research commonly focuses on brain signal variability as an indicator of the capability to explore different network constellations. For example, our group has shown that brain signal variability is reduced in the damaged versus contralateral hippocampus in mTLE (Protzner, Valiante et al. 2010) and that MTL variability can be linked to individual differences in a meaningful behavioral outcome (Protzner, Kovacevic et al. 2013). Instead of focusing on direct variability measures, in the current study, we examined functional connectivity changes supporting different cognitive tasks. Importantly, our current data are in agreement with these ideas, and suggest that reduced variability is reflected in inflexible functional connectivity patterns despite changing task conditions in mTLE. However, further research is necessary to directly test the relationship between reduced brain noise and restricted range of functional connectivity fluctuations. For example, it would be interesting to examining resting state fMRI in patients with mTLE using a sliding window approach to test whether the explorations of subnetworks commonly seen in
healthy controls would be markedly subdued in patients with mTLE. From this perspective, it is further interesting to note that others have reported the structural network topology in patients with mTLE to be different from that in controls by showing a more stable, regular network (Bernhardt, Chen et al. 2011; Bernhardt, Hong et al. 2013). Although the relationship has not yet been examined directly, an interesting research question would be whether the regular structural network topology in mTLE can account for the more stable functional connectivity patterns observed here.

Surprisingly, we observed more negative functional connectivity in patients with left mTLE than in healthy controls during both AM stages. These negative correlations affected only hippocampal-neocortical and not intra- or interhippocampal connectivity. While there are no direct data that speak to these findings during task performance, negative correlations between the damaged MTL and other brain regions have been reported in fMRI resting state studies (Morgan, Gore et al. 2010). It might be that these extensive negative correlations reflect the dysfunctional relationship between both MTL and neocortex. In the current study, we aimed to examine how unilateral damage to the MTL affects hippocampal-neocortical networks during AM construction and elaboration. Therefore, we specifically examined a network that supported these conditions in healthy controls, forcing patient data into a hippocampal-centric network. Using this approach, we were able to show that the damaged hippocampus does not support the flexible switch between these networks as seen in healthy controls.

Further in agreement with our interpretation that the hippocampal system is disengaged from the AM retrieval process in patients with mTLE and consistent with other studies examining AM retrieval and other episodic memory tasks in mTLE, we found that ipsilateral MTL activation in patients with mTLE was markedly reduced in comparison to healthy controls (Detre, Maccotta et al. 1998; Dupont, Van de Moortele et al. 2000; Jokeit, Okujava et al. 2001; Addis, Moscovitch et al. 2007; McAndrews and Cohn 2012; St-Laurent 2012). Further suggesting that the hippocampal system is disengaged during AM retrieval in patients with mTLE, a previous study showed increased connectivity between the RSP and amPFC during AM retrieval in patients with left mTLE in comparison to healthy controls (Addis, Moscovitch et al. 2007). In the current model, we adopted the same model that showed connectivity differences between AM construction and elaboration in healthy controls (see Chapter 5). Thus, we did not include cortico-cortical connections and no node in the PCC/RSP. We therefore could not compare these
models directly. Interestingly however, we found that patients with left mTLE showed greater AM retrieval activation in prefrontal and lateral temporal cortices than healthy controls, indicating a possible alternative route to AM retrieval in patients with MTL damage.

Our findings further speak to behavioral studies showing a qualitative difference between AM retrieval in patients with mTLE and healthy controls (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011). Our results suggest that patients with L-mTLE might be able to construct AMs but even this early AM stage might be supported by a different network in patients than in healthy controls. That is, AM construction in left mTLE is clearly not supported by a strong left hippocampal-fronto-temporal network. In our data for example, functional connectivity between the left anterior hippocampus and medial PFC was positive during construction and elaboration in healthy controls, however, in patients with L-mTLE this connection was strongly negative during construction and negligible during elaboration. Speculatively, it could be that patients with MTL damage select different kinds of AMs, for example more personal relevant ones that are more firmly embedded into the self-knowledge structure. In this scenario, seeding from a different brain region might be a better approach to studying networks underlying AM retrieval in mTLE. A candidate region for such an approach would be the vmPFC which has recently gained some attention for its potential role in supporting schematic information (van Kesteren, Rijpkema et al. 2010; Ghosh and Gilboa 2013). Although speculative, seeding from the vmPFC in addition to collecting detailed information about the AM being retrieved might illustrate whether patients with mTLE retrieve mainly personally semantic AMs and whether this construction process is supported by vmPFC connectivity to possibly other semantic relevant areas such as the LTC and TempP. Further, AM elaboration in patients with mTLE might also rely more on semantic visual-perceptual details that describe the typical rather than specific appearance of objects. Here, it might be that such an elaboration process is supported by vmPFC connectivity to visual-perceptual brain regions.
6.5 Conclusions

Here, we follow up on our earlier study (see Chapter 0) by examining how unilateral MTL damage affects the complex hippocampal-neocortical interplay during construction and elaboration of AM. We found that damage to the left MTL drastically reduced the translation of intra- and interhippocampal connectivity to adapt flexibly to different cognitive demands. These findings support emerging evidence that brain signal variability reflects functional integrity of neuronal systems and adds that reduced variability might be expressed during task-based fMRI as inflexible functional connectivity patterns which in turn might inhibit the typical flexible behavioral repertoire.
7 General Discussion
The data presented in the current thesis provide evidence that formal network analyses are essential to understand the relationship between large-scale neurocognitive networks underlying cognitive functions and their relevance in clinical settings. The main focus of this thesis was to examine hippocampal-neocortical networks supporting episodic memory and to characterize the relationship of changes in structural integrity to functional connectivity parameters and episodic memory impairments in patients with unilateral damage to the MTLs. The following section briefly recapitulates the main findings of this thesis. Afterwards the general discussion will review the main findings presented in the light of the three major themes of the literature review: hippocampal-neocortical network disruptions in patients with mTLE, hippocampal-neocortical networks underlying episodic memory and networks of the brain.

7.1 Summary of Findings

The first study investigated how unilateral mTLE affects connectivity of the DMN and whether these disruptions can be exploited clinically to characterize memory deficits pre- and postsurgically. Using fMRI resting state scans and clinical memory assessments, we showed that patients with mTLE have reduced functional connectivity from the PCC to the affected hippocampus and increased PCC connectivity to the contralateral hippocampus. Further, stronger PCC connectivity to the epileptogenic hippocampus was associated with better presurgical memory performance and greater postsurgical memory decline. Stronger PCC connectivity to the contralateral hippocampus on the other hand was associated with less postsurgical memory decline. Of special interest, following epilepsy surgery PCC connectivity to the remaining hippocampus increased from presurgical connectivity strength and also showed enhanced correlation with postsurgical memory function. We further demonstrated that connectivity between these regions predicted memory outcome more accurately than predictors that are frequently relied upon in the clinical literature, including hippocampal volume and presurgical memory performance.
The second study followed up on the results of the first study. Here, we investigated the extent of structural damage due to unilateral mTLE, how this damage relates to functional connectivity changes within the DMN, and the relationship between structural damage, functional connectivity changes and episodic memory capacity. Whereas the first study concentrated mainly on PCC-HC connection, here we examined patterns of structural alterations and functional connectivity changes throughout the entire DMN. We found that structural damage, operationalized as GMV loss measured with VBM, in patients with mTLE was mostly confined to the affected MTL and neighbouring ROIs situated in the LTC. In contrast to the reasonably focal structural damage, we found widespread bilateral functional connectivity alterations in patients in comparison to healthy controls. Specifically, patients with mTLE showed reduced connectivity between both MTLs and the posterior part of the DMN, and increased long-range connectivity mainly involving the ROIs situated in the PFC and medial and lateral parietal cortices. Importantly, these patterns were also associated with episodic memory capacity in patients with mTLE, in that the pattern that was more similar to controls was associated with better episodic memory capacity whereas the ‘alternate’ pattern of connectivity was associated with worse memory capacity. Interestingly, structural damage alone did not predict episodic memory capacity; however, a mediation analysis revealed that functional connectivity changes mediated the relationship between structural damage and episodic memory capacity.

In studies three and four, the focus was on activation and connectivity in AM retrieval rather than resting state. The third study concentrated on the hippocampus as a hub coordinating transient networks that underlie different stages of AM retrieval. Here, we acquired fMRI data in healthy participants who were asked to retrieve specific AMs of their lives. Importantly, they were asked to indicate with a button press when they had a specific incident in mind and started to mentally re-experience this event. This experimental design enabled us to distinguish two AM stages, construction and elaboration, and to examine how hippocampal-neocortical interactions change according to these different cognitive demands. We found that the left hippocampus interacted with fronto-temporal regions during construction and with occipito-temporo-parietal regions during elaboration. Further examining the specific contributions of the anterior and posterior segments of the hippocampi, we found that the left anterior hippocampus interacted mainly with the left PFC during AM construction and both posterior hippocampi with visual-perceptual regions during AM elaboration. Lastly, we found a new and interesting
intrahippocampal dialogue in that both anterior segments influenced activity in both posterior segments to a greater extent during construction than elaboration.

The fourth study examined whether the capacity of the hippocampus to coordinate these transient networks underlying AM retrieval is affected in patients with left mTLE, using the same protocol as in study three. Replicating a previous study from our laboratory (Addis, Moscovitch et al. 2007), we found reduced recruitment of the left hippocampus during AM retrieval in patients compared to healthy controls. We then examined functional connectivity of patients with mTLE within the same neuronal network that supported AM construction and elaboration in healthy controls. Whereas in controls, the pattern of functional connectivity differed between AM construction and elaboration, confirming the flexibility of the hippocampus to resume different network constellations, functional connectivity measures in patients with mTLE did not change between these two AM retrieval stages. This result suggests that the capacity of the epileptogenic hippocampus to coordinate transient neocortical networks might be restricted, which may underlie the reduced ability to support the retrieval of detail-rich AMs we and others have observed in patients with mTLE (Viskontas, McAndrews et al. 2000; Voltzenlogel, Despres et al. 2006; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011).

7.2 Hippocampal-Neocortical Network Disruptions in Patients with mTLE

7.2.1 Structural Integrity of the Epileptogenic MTL and its Relationship to Episodic Memory Capacity

In agreement with the vast majority of other studies examining VBM in patients with mTLE (Walker, Chan et al. 2007; Keller and Roberts 2008; Richardson 2010), we found reduced GMV in the ROI situated in the ipsilateral hippocampus, providing further evidence that structural damage of the epileptogenic hippocampus is the hallmark lesion of mTLE. In both left and right mTLE cases, we also found GMV reductions in the adjacent ipsilateral parahippocampal and lateral surface of the temporal cortex, supporting the proposal that structural damage is not solely
confined to the affected MTL (Bell, Lin et al. 2011; Bernhardt, Hong et al. 2013). Nonetheless, we did not observe GMV alterations outside the affected temporal lobe, which stands in contrast to some studies showing extensive reductions in GMV and cortical thickness in these patients (Lin, Salamon et al. 2007; Bernhardt, Worsley et al. 2008; Bernhardt, Bernasconi et al. 2010). As suggested before, these differences could either be a result of different sample sizes and thresholding (Bernasconi, Duchesne et al. 2004; Bouilleret, Semah et al. 2008; Pell, Briellmann et al. 2008), but also in our study, we focused specifically on small ROIs within the DMN, therefore excluding most of the regions that commonly show structural alterations, such as the thalamus and insula (Keller and Roberts 2008; Keller, O'Muircheartaigh et al. 2014).

In our data, we did not observe a direct relationship between hippocampal volume and episodic memory capacity. This finding disagrees with several studies showing a positive relationship between hippocampal volume and episodic memory in healthy controls (Poppenk and Moscovitch 2011) and patients with mTLE (Rausch 1987; Trenerry, Jack et al. 1993). However, the relationship between hippocampal volume and episodic memory is not as straightforward as one might think. In fact, a meta-analysis in healthy controls examining this relationship indicates that the common hypothesis, “bigger is always better” should be rejected as in some cases even the opposite, “smaller is better” seems to fit the data better (Van Petten 2004). Studies that do show a positive relationship used differential measures of GMV, such as the ratio between anterior and posterior segments of the hippocampus in healthy controls (Poppenk and Moscovitch 2011) or the difference between left and right hippocampal volume in patients with mTLE (Trenerry, Jack et al. 1993). Nonetheless, hippocampal volume or the presence or absence of MTL sclerosis is one of the most powerful predictors of postsurgical memory outcome in patients with mTLE (Elshorst, Pohlmann-Eden et al. 2009; Bell, Lin et al. 2011). Therefore, a better account for structural integrity’s contribution to behavior might be a mediating effect of functional integrity measures (see also 4.4.3). For example and as our fourth study suggest, structurally intact hippocampal tissue might enable the rich functional repertoire needed to support flexible episodic memory capacity, whereas structural damage restricts this functional flexibility.
7.2.2  Functional Integrity of the Epileptogenic MTL and its Relationship to Episodic Memory Capacity

As previously reported by our group and others, here we replicate that patients with unilateral mTLE show reduced MTL activation during AM retrieval (Addis, Moscovitch et al. 2007; McAndrews and Cohn 2012; St-Laurent 2012). This reduction is most dramatic in the ipsilateral hippocampus which is in agreement with other studies showing reduced ipsilateral MTL recruitment during navigating through a familiar environment (Jokeit, Okujava et al. 2001), and encoding patterns, faces, scenes, and words (Golby, Poldrack et al. 2002). Further, a few studies have shown that hippocampal activation correlates with episodic memory measures (Addis, Moscovitch et al. 2004; St-Laurent 2012; St Jacques, Rubin et al. 2012). In agreement with these findings, a growing body of evidence suggests that in patients with mTLE, the level of MTL recruitment can be used as a predictor of postsurgical episodic memory outcome (Rabin, Narayan et al. 2004; Richardson, Strange et al. 2004; Powell, Richardson et al. 2008; Bonelli, Powell et al. 2010). However, others failed to show a relationship between presurgical MTL activation and postsurgical memory outcome (Binder, Swanson et al. 2010) and McAndrews & Cohn conclude in a recent review (McAndrews and Cohn 2012) that it is still unclear whether fMRI parameters provide independent predictive power to the prediction of memory outcome. Also, the relationship between hippocampal activation and episodic memory might become difficult to predict in patients with structural damage to the hippocampus as structural damage and functional activation do not always follow a linear relationship (Sawrie, Martin et al. 2000; Dickerson, Salat et al. 2004). That is, this nonlinear function results at least in some cases in paradoxically increases in hippocampal activation in patients with mTLE (Guedj, Bettus et al. 2011).

Together, studies focusing on the MTL in patients with mTLE have consistently shown reduced structural (i.e., GMV loss) and functional (i.e., reduced fMRI activation) integrity of the epileptogenic hippocampus and surrounding cortices. However, it appears that these regional measures of structural or functional MTL integrity can only explain a small to medium percentage of variance of episodic memory capacity in mTLE. In fact, I have argued throughout this thesis, that hippocampal-neocortical network integrity might be a better indicator of episodic memory capacity in this patient population.
7.2.3 Decreased DMN Connectivity in Patients with mTLE

In contrast to the reasonably focal structural damage, we found widespread functional connectivity changes in patients with unilateral mTLE. Especially the connections between both MTLs and the posterior part of the DMN including the RSP cortex and PCC were significantly reduced in patients with mTLE in comparison to healthy controls. In agreement, the majority of fMRI resting state studies in patients with mTLE report similar findings, reduced connectivity between the MTLs and PCC/RSP (Waites, Briellmann et al. 2006; Zhang, Lu et al. 2009; Morgan, Gore et al. 2010; Pereira, Alessio et al. 2010; Morgan, Rogers et al. 2011; Holmes, Folley et al. 2012; Pittau, Grova et al. 2012; Doucet, Osipowicz et al. 2013; Holmes, Yang et al. 2013; Ji, Zhang et al. 2013; Kucukboyaci, Kemmotsu et al. 2013; Maccotta, He et al. 2013; Trotta, Goldman et al. 2013; Haneef, Lenartowicz et al. 2014). This disconnection of the affected MTL from the PCC/RSP appears to be directly linked to structural changes. In our study, we could show that functional connectivity changes were associated with the extent of structural damage. This finding is in agreement with another study showing that GMV loss accounted for the reduction in functional connectivity specifically between the MTL and posterior part and not between the MTL and anterior part of the DMN in patients with mTLE (Voets, Beckmann et al. 2012). Lastly, also white matter integrity along tracts connecting the hippocampus and RSP appears to be reduced in this patient population (Liao, Zhang et al. 2011). However, neither in ours nor in any other study has the PCC/RSP been implicated directly to suffer structural changes due to mTLE. In agreement with this proposal, we could show using graph theoretic degree metrics on functional connectivity matrices that the PCC remained the main hub of the DMN in patients with mTLE whereas the affected hippocampus was disconnected from the rest of the DMN (see Figure 3.2). Together, these findings suggest that the functional connectivity disruptions between PCC and hippocampus are likely caused by structural damage to the MTL itself and connecting fibres to the PCC, rather than structural changes of the PCC/RSP complex.

Importantly, in this thesis, we could show for the first time that the connection between the posterior part of the DMN and both MTLs explained a considerable amount of variance in episodic memory performance in patients with mTLE. While the first study of this thesis showed that stronger connectivity between the PCC and epileptogenic hippocampus was associated with better presurgical memory performance and greater postsurgical decline, the second study extended these findings in demonstrating that connectivity of the entire DMN predicted
presurgical memory performance even more accurately than just PCC-HC connectivity. These findings speak to the general idea that episodic memory is supported by brain wide networks and that the integrity of these networks are in fact better indicators of episodic memory capacity than local integrity or connectivity (McIntosh 2000).

Further, it is interesting to note that especially the connections between the MTL and posterior parts of the DMN predicted episodic memory capacity, as this finding is generally in line with studies proposing that recruitment of and connectivity between posterior nodes of the DMN is crucial for episodic memory function (Vincent, Snyder et al. 2006; Shapira-Lichter, Oren et al. 2013). From this perspective, the disruption of the connectivity between bilateral hippocampus and posterior neocortical regions may be at the center of the patients’ impairment at recovering specific details of AMs (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011).

### 7.2.4 Increased DMN Connectivity in Patients with mTLE

The converse of the reduced functional connectivity between the MTL and posterior part of the DMN was the increased connectivity between the PCC and the unaffected hippocampus in the first study and between the ROIs situated in the PFC and posterior cortices, such as lateral parietal cortex in the second study of this thesis. Of note, we replicated the increase between PCC and contralateral hippocampus (using a whole volume hippocampal mask) in the second study as well; however, restricting our analysis to ROIs of the DMN, we did not see this increase between the PCC and ROI situated within the contralateral hippocampus. Nonetheless, increased functional connectivity has been reported in a growing number of studies examining resting state networks in patients with mTLE (Bettus, Bartolomei et al. 2010; Morgan, Rogers et al. 2011; Maccotta, He et al. 2013; McCormick, Quraan et al. 2013). However, the spatial extent and localization of the increases are quiet variable. For example, Bettus et al. (Bettus, Bartolomei et al. 2010) found increased functional connectivity within the contralateral MTL, and Maccotta et al. (Maccotta, He et al. 2013) within the ipsilateral hemisphere. We argue in the second study of this thesis that this variability is mainly due to the different approaches to evaluate these increases. That is, most resting state studies examine functional connectivity based on a seed placed in the ipsilateral hippocampus/MTL and contralateral hippocampus/MTL (Pereira, Alessio et al. 2010; Morgan, Rogers et al. 2011; Holmes, Folley et al. 2012; Pittau, Grova et al. 2013).
2012; Doucet, Osipowicz et al. 2013; Ji, Zhang et al. 2013; Kucukboyaci, Kemmotsu et al. 2013; Maccotta, He et al. 2013; Trotta, Goldman et al. 2013; Haneef, Lenartowicz et al. 2014). Using this approach, one can evaluate the degree to which the MTLs are disconnected from the rest of the brain, however, connections between brain regions outside the MTLs cannot be evaluated. Thus, seeding from outside the MTL damage, for example from the PCC as a main hub of the brain or taking into account all possible connections between relevant nodes, might reveal a more accurate picture of reduced and increased functional connectivity associated with mTLE. Indeed, studies seeding from the amPFC for example show increased connectivity to the LTC and medial and lateral parietal cortices (Waites, Briellmann et al. 2006; Haneef, Lenartowicz et al. 2012). Further, a study using 90 cortical and subcortical ROIs demonstrated widespread reductions but particular increases of functional connectivity between parietal and frontal cortices in patients with mTLE in comparison to healthy controls (Liao, Zhang et al. 2010). Together, these findings are in agreement with our findings that functional connectivity between the PFC and lateral temporal and parietal cortices is increased in patients with mTLE.

To our knowledge, our study is the first to relate these increases to episodic memory capacity in these patients. While none of the current literature speaks to this pattern directly, a few recent observations allow for some speculation. For example, Addis et al. (Addis, Moscovitch et al. 2007) examined networks underlying AM retrieval in patients with mTLE and found that long range effective connectivity between the RSP cortex and amPFC was increased in patients with mTLE in comparison to healthy controls, indicating that this connection might indeed be meaningful to episodic memory function in patients. Further, another study in our lab found that patients with mTLE activated generally the same language network as healthy controls but behavioral performance on a word retrieval task correlated with different networks in the two groups (Protzner and McAndrews 2011). Together, these findings suggest that patients with mTLE rely on different neuronal networks to support cognitive tasks that typically engage the MTLs in healthy controls. The implications of these findings target primarily the clinical realm, hoping that understanding functional network changes might help to predict postsurgical memory outcome. The first study of this thesis speaks directly to this issue. Here, we found that connectivity between the PCC and the contralateral hippocampus was increased in patients with mTLE in comparison to healthy controls and that stronger connectivity was associated with less postsurgical memory decline. Corroborating this finding, connectivity between the PCC and
contralateral hippocampus increased postsurgically in comparison to presurgical connectivity strength and was now associated with better postsurgical memory performance. These findings provide strong evidence that these increases in connectivity reflect neuroplasticity supporting the functional reserve of the contralateral MTL.

7.2.5 Flexible Network Changes in Patients with mTLE: Neuronal Context

In the fourth study of this thesis, we found that patients with mTLE did not show dynamic fluctuations in functional connectivity patterns between AM construction and elaboration phases as was seen in healthy controls. To our knowledge, this is the first observation of this lack of functional dynamics in patients with mTLE during task performance. Speculative, this reduced flexibility might be a result of reduced brain signal variability. As has been shown previously (Protzner, Valiante et al. 2010), iEEG signal of the affected hippocampus showed reduced variability relative to the contralateral hippocampus. These findings are in line with empirical data and computational simulations suggesting that brain signal variability measures the degree of which a neural system explores possible network configurations and that might ultimately reflect functional integrity (Honey, Kotter et al. 2007; Ghosh, Rho et al. 2008; Garrett, Kovacevic et al. 2010; McIntosh, Kovacevic et al. 2010; Misic, Mills et al. 2010; Deco, Jirsa et al. 2011). Additionally, reduced variability in BOLD signal was a trait in mTLE that predicted memory performance better than even activation during an AM retrieval task (Protzner, Kovacevic et al. 2013). In other words, mTLE might lead to a lack of functional integrity expressed as less functionally variable tissue which results in a stable pattern of functional connectivity despite changing cognitive states. From this perspective and in agreement with resting state studies showing a disconnection of the hippocampus from other regions of the brain, our findings here might reflect the disengagement of the hippocampal system from the rest of the DMN even during active task demands.

7.2.6 Alternative Networks supporting AM Retrieval in Patients with mTLE

There are indeed some indications in the literature that patients with mTLE rely on alternative, non-hippocampal-centric, networks possibly comprising long-range connections between the PFC and RSP cortex to support the retrieval of AMs (Addis, Moscovitch et al. 2007). In
agreement with this proposal, we found greater activation in the right vmPFC and LTC during AM retrieval in patients with mTLE in comparison to healthy controls. As resting state connectivity between those same regions predicted poor episodic memory in patients with mTLE, one might expect patients with mTLE to show increased connectivity between the vmPFC and LTC when retrieving AMs. The vmPFC has recently attracted a considerable amount of attention in that this region might be essential to form and organize schematic and personal relevant information (van Kesteren, Ruiter et al. 2012; Ghosh and Gilboa 2013; Preston and Eichenbaum 2013). For example, Roy et al. (Roy, Shohamy et al. 2012) speculate that the vmPFC might integrate informational elements from a wide variety of brain systems, including sensory, affective and long-term memory systems. In the context of this thesis, one can imagine that the vmPFC in healthy controls is strongly connected to the hippocampus during AM retrieval, thus retrieving specific, detail-rich AMs, whereas in patients with mTLE, the vmPFC might be connected to regions such as the LTC, supporting the retrieval of schematized AMs observed in this patient population (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011).

7.2.7 Clinical Relevance of Network Integrity in Patients with mTLE

A major contribution of this thesis to the literature on patients with mTLE is the potential clinical use of hippocampal-neocortical network parameters in the prediction of memory outcome. Here, the first study of this thesis provides direct evidence that connectivity between the PCC and bilateral hippocampus indicates episodic memory capacity in these patients. Further, the second study extends these findings to suggest that functional connectivity changes throughout the DMN might be an even better indicator of episodic memory capacity than just one connection. In fact, we could show that these effects are specific to episodic memory and that DMN connectivity for example did not predict IQ measures. Further, functional connectivity measures predicted episodic memory capacity more accurately than standard predictors, such as hippocampal volume and presurgical memory performance. Lastly, using functional connectivity we were able to evaluate not only functional adequacy of the affected MTL but also the functional reserve of the contralateral MTL. The last study of this thesis primarily focused on the hippocampal-neocortical networks underlying different AM retrieval stages in patients with mTLE. Unfortunately, limited amount of data on postsurgical patients prevented us from predicting memory outcome based on measures of the dynamic range of hippocampal functional
connectivity. To speculate, one would expect that a greater dynamic range of hippocampal functional connectivity would be associated with better presurgical memory performance but also with a steeper decline in memory capacity postsurgically.

Nonetheless, the clinical benefits of the results of this thesis for patients who are candidates for epilepsy surgery are obvious. Specifically, these functional connectivity measures may become an accurate measure of the risk of postsurgical memory decline in this patient population. As pointed out by others as well, it is important to remember the subjective experience of the patients in the search for these accurate predictors (Baxendale and Thompson 2005). That is, some patients complain about memory problems postsurgically that are not reflected in their formal neuropsychological testing (Baxendale and Thompson 2005). However, examining brain network parameters that support a wide variety of episodic memory tasks in healthy individuals such as the integration of the MTLs into the DMN might be a good start to capture what lies at the heart of episodic memory and in that respect, hopefully at the heart of subjective experiences described by patients with mTLE.

7.3 Hippocampal-Neocortical Networks underlying Episodic Memory

7.3.1 Fractionation of Hippocampal Contribution to Autobiographical Memory

The role of the hippocampus in episodic and autobiographical memory is well established and our finding that bilateral hippocampal activation supports AM retrieval in healthy controls is no exception (Addis, Wong et al. 2007; McDermott, Szpunar et al. 2009). However, several findings of the current thesis in terms of hippocampal contribution to AM retrieval are worth noting. For example, we found early left hippocampal activation during AM construction and sustained bilateral hippocampal activation during AM elaboration (see Figure 5.1). This finding leads to the question whether the left and right hippocampus contribute differently to AM retrieval. Typically, AM retrieval elicits a pattern of either left or bilateral hippocampal activation (Maguire 2001; Svoboda, McKinnon et al. 2006). As St-Laurent (St-Laurent 2012)
notes, AM tasks that tap into more factual self knowledge typically generate more left lateralized activation (Maguire 2001; Svoboda, McKinnon et al. 2006; McDermott, Szpunar et al. 2009), whereas AM tasks that require retrieving recent or emotional AMs or allotting more time for AM retrieval generate more bilateral hippocampal activation (Maguire and Frith 2003; Svoboda, McKinnon et al. 2006; Cabeza and St Jacques 2007). St-Laurent (St-Laurent 2012) further speculates that left hippocampus might be essential to access and reconstruct an episode and the right hippocampus contributes experiential details to the retrieved memory. Whereas the mean activation analyses of our ST-PLS would support the importance of the left hippocampus for AM construction processes, our SEM analysis in healthy controls indicates that both AM retrieval stages, construction and elaboration are supported by a dialogue between both hippocampi and other neocortical regions (see Figure 5.5). As pointed out above, this complex interhemispheric dialogue might explain why patients with mTLE have difficulties to retrieve AM details no matter whether the epileptogenic focus is in the left or right MTL.

Further, our findings that especially the posterior segments of both hippocampi, in coordination with visual-perceptual regions, support the retrieval of episodic details is in agreement with recent advances illustrating a functional dissociation between the anterior and posterior segments of the hippocampus and have been discussed previously in the third study. Here, the general idea in terms of AM is that the anterior hippocampus supports global associations between main actors and spatial layout, whereas the posterior hippocampus might support fine grain visual-perceptual details of individual episodic elements (Poppenk, Evensmoen et al. 2013). Our data are the first to empirically support this distinction in that the anterior hippocampus showed greater connectivity with fronto-temporal regions during AM construction and the posterior hippocampus greater connectivity with occipito-temporo-parietal regions during elaboration.

7.3.2 Hippocampus as a Critical Hub for Episodic Memory

The second major contribution of this thesis is the discovery that the hippocampus coordinates transient networks involving different brain regions to support different episodic memory demands. This finding provides evidence that the hippocampus can be seen as the critical hub structure to support episodic memory in the brain. Whereas other studies have shown that the hippocampus can form parts of different memory networks during encoding versus retrieval (McCormick, Moscovitch et al. 2010), and during episodic versus semantic retrieval (Rajah and
McIntosh 2005), our data here reveal that the hippocampus connects with separate sets of brain regions during different stages of the same AM trials. That is, the left anterior hippocampus was functionally connected to a fronto-temporal network during AM construction and a widespread temporo-parieto-occipital network during AM elaboration. As discussed previously, these findings provide striking evidence in support of Conway’s model of AM organization and further clarify which brain regions are implicated in the different stages of AM retrieval (Conway, Turk et al. 1999; Conway and Pleydell-Pearce 2000; Conway, Pleydell-Pearce et al. 2001; Conway, Pleydell-Pearce et al. 2003; Conway 2009). The novel finding of our data is the critical function of the hippocampus to coordinate this network dialogue during both AM construction and elaboration.

Extrapolating from our results here, it may be a reasonable expectation that the connectional fingerprints of the hippocampus reach out to most neocortical areas of the brain and that different patterns of functional connectivity might support different kinds of cognitive tasks, such as implicit (Henke, Weber et al. 1999; Henke, Treyer et al. 2003) and short-term memory (Olsen, Nichols et al. 2009). In fact, current scientific debates about the differential contributions of MTL substructures attribute a specific process to the hippocampus, that is binding items in context (Ranganath 2010). Therefore, rather than the episodic memory hub, the hippocampus might be more accurately described as the contextual binding hub in the brain. From that perspective, our results could be interpreted as that the left hippocampus in collaboration with fronto-temporal regions typically involved in semantic and schematic memory retrieval binds information about the general outline of an AM during the construction phase. Then, once a specific AM is retrieved, hippocampal connectivity to visual-perceptual brain regions supports the binding of episodic elements into this general outline into a vivid, detail-rich mental representation. This interpretation agrees with the idea of the neuronal context in that hippocampal connectivity depends on the current cognitive demand (McIntosh 1999; McIntosh 2000) and agrees with the model that the hippocampus forms process specific alliances to support distinctive cognitive tasks (Moscovitch 1992; Cabeza and Moscovitch 2013).

### 7.3.3 The Default Mode Network and Episodic Memory

A current debate in the literature concerns the function of the DMN in active cognition. For example, in the attempt to capture the commonality of typical DMN activation, that is
remembering, thinking about the future, and thinking about another person’s perspective, Buckner (Buckner 2012) hypothesizes that the DMN might support “... the ability to shift from perceiving the immediate environment to building a mental model, perhaps to be considered a simulation, of an alternative scenario”. On the other hand, Deco et al. (Deco, Jirsa et al. 2011) argue that “... such a cognitive interpretation is difficult to uphold in light of the observations that these [resting state] patterns also exist in the absence of consciousness during anesthesia and sleep”. Whereas the main focus of this thesis was not to test either hypothesis, our data might contribute some insight to this debate. For example, we found that DMN connectivity in patients with mTLE was associated specifically with episodic memory capacity and not, for example, with IQ measures, indicating some specificity of the DMN to episodic memory and therefore supporting Buckner’s (Buckner 2012) hypothesis about a specific cognitive function of the DMN. However, it is important to keep in mind that we used clinical memory measures that are composite scores of neuropsychological tasks directed to capture episodic memory and not recollection or subjective simulations on which tasks Buckner’s (Buckner 2012) hypothesis is built. Nonetheless, our results are in agreement with other studies showing active DMN response to cognitive tasks involving these kinds of mental time travel (Addis, McIntosh et al. 2004; Andrews-Hanna, Reidler et al. 2010; Rugg and Vilberg 2013). On the other hand, our data also support Deco’s et al. (Deco, Jirsa et al. 2011) hypothesis. In fact, we found that DMN changes could be attributed to structural damage. Specifically, functional connectivity alterations mediated the effect of structural damage on episodic memory capacity. These findings suggest that indeed, DMN connectivity measured over a six minute resting state scan in patients with mTLE reflects anatomical changes of regional decline in grey matter volume and possibly underlying white matter tracks between the MTL and other DMN regions. Further, we could show that functional connectivity patterns of the hippocampus as a node of the DMN at a shorter timescale, that is during construction and elaboration of AMs, differ substantially from the commonly referred to “AM network” that resembles the DMN so closely (Addis, McIntosh et al. 2004; Spreng, Mar et al. 2009; Spreng and Grady 2010).

In sum, the data presented here support both hypotheses from Buckner (Buckner 2012) and Deco et al. (Deco, Jirsa et al. 2011). It might be reasonable to assume that the strong structural connectivity of the DMN constrains functional connectivity if measured over a longer period of time or during anesthesia (Vincent, Patel et al. 2007) and early stages of sleep (Fukunaga,
Horovitz et al. 2006; Picchioni, Duyn et al. 2013). In addition, we know from a substantial body of neuroimaging and lesion data that each of the DMN regions contributes specific aspects to human cognition, for example, the MTL supports associative binding processes (Eichenbaum, Yonelinas et al. 2007; Dickerson and Eichenbaum 2010; Ranganath 2010), and the amPFC self-referential processes (Amodio and Frith 2006; Svoboda, McKinnon et al. 2006; Abraham 2013) etc. From this perspective, the DMN might indeed be a collection of hubs that in sum support a variety of cognitive functions at the center of human behavior, such as autonoetic consciousness (Tulving 1973; Tulving 2002). However, at individual time points within that stream of consciousness, the connectivity within and beyond the DMN varies considerably as has been shown by resting state studies examining moment-to-moment connectivity (Honey, Kotter et al. 2007; Kiviniemi, Vire et al. 2011; Jones, Vemuri et al. 2012; Kucyi, Salomons et al. 2013). Thus, these transient network formations most likely support specific incidents of remembering or thinking about the future. From this perspective, there is no individual network supporting remembering of specific episodic memories, rather transient network constellations form around functionally specialized brain regions that enable the reconstruction of transient mental re-experiences or future simulations confined to the current moment.

7.4 Networks of the Brain

7.4.1 Functional Network Consequences of Local Structural Damage

The typical way to frame the goal of the Human Brain Connectome is to say that this project aims to map the structural connectome of the human brain, so that in the future, one can make predictions about functional network changes in the presence of specific structural damages (Sporns, Tononi et al. 2005; Sporns 2013). However, patients who have local structural damage can also inform us about the consequences of this damage on functional networks and how these network changes relate to behavior. In the current thesis, for example, we showed that reasonably localized unilateral structural damage to the MTL leads to a disconnection of the affected MTL from the rest of the DMN (measured by graph theoretical degree, see Figure 3.2) but also to widespread bilateral functional connectivity changes (see Figure 4.1). This finding is
in agreement with computational simulations predicting widespread changes following damage to a DMN node (Alstott, Breakspear et al. 2009; van den Heuvel and Sporns 2011). In fact, the patterns of functional connectivity changes we observed here followed predictions of these computational models in that we found a) decreased degree of functional connectivity of the affected node b) other decreases of interhemispheric connections and c) increased intrahemispheric, anterior-posterior directed functional connectivity. One aspect of these changes is therefore, that structural damage leads to isolation of the affected region. Interestingly, within the epileptogenic zone, functional connectivity might be within ranges of healthy tissue. For example, a study examining functional connectivity within and between the primary epileptogenic and unaffected regions in patients with mTLE confirmed a decrease between but no difference within these zones (Bettus, Ranjeva et al. 2011). In agreement, we found stable intrahippocampal connectivity that in strength did not differ from healthy controls. In sum, despite reduced signal variability, a lack of fluctuations between cognitive states, and a disconnection of the affected region, functional connectivity within the epileptogenic region might be indistinguishable from healthy controls. This observation indicates that in order to evaluate widespread consequences of local structural damage on functional networks, it might be better to examine the entire functional connectivity matrices rather than seeding from the damaged region.

From this perspective, it is of further interest that the hippocampus is not only part of the DMN (Buckner, Andrews-Hanna et al. 2008) but also part of the rich club of the brain (van den Heuvel and Sporns 2011). Regions of this rich club are structurally high-degree nodes that are more densely interconnected with each other than predicted by chance. As more studies are undertaken examining the functional role of these rich club members, it is becoming apparent that the brain’s rich club might serve as a macroscopic anatomical substrate to cross-link functional networks and therefore might play an important role in the integration of information between segregated functional domains of the human cortex (van den Heuvel and Sporns 2013). In agreement with this idea, a recent study simulated how signal units flow between grey matter nodes along white matter paths (Misic, Sporns et al. 2014). Much of the global communication was mediated by rich club members, indicating a critical role of the rich club in functional dynamics. Of note, that study further examined network statistics under the condition of elevated network traffic and found that the MTL, together with the amPFC and PCC/RSP cortex, was among the few brain
regions showing the greatest information traffic, indicating that the MTL might be a critical node for global information flow. These findings accord well with our results that damage to the MTL causes functional network changes far beyond the affected site which has implications for explaining behavioral variance specific to that network.

7.4.2 Functional Neuronal Networks enabling Cognition

Throughout this thesis, I have argued in line with the idea that complex cognitive functions such as episodic memory do not rely on a single brain region but on interactions with many brain regions, each contributing unique processes to the overall behavior (McIntosh 1999; McIntosh 2000). The data presented in the empirical chapters undergird this notion. That is, PCC-HC and even more so DMN connectivity could predict episodic memory capacity more accurately than any individual parameter for MTL dysfunction, such as hippocampal volume, and presurgical memory performance. Further, in the third study of this thesis, we were able to identify complex hippocampal-neocortical interactions supporting two different cognitive stages. It is therefore a reasonable expectation that other large-scale neurocognitive networks might predict the cognitive capacity for which they are specific. Indeed, resting state connectivity among brain regions typically associated with language abilities positively correlated with reading abilities in young adults (Koyama, Di Martino et al. 2011). Therefore, our data here support the idea that cognition emerges through network interactions (McIntosh 1999; McIntosh 2000) and that formal multivariate network analyses, in comparison to univariate mean based analyses, are best suited to assess functional integrity of a cognitive system.

Further, our data are in agreement with the idea that the anatomical skeleton of the human brain shapes and constrains the extensive functional repertoire which in turn enables the expression of such rich behavioral variability (Sporns, Tononi et al. 2005; Deco, Jirsa et al. 2011; Nakagawa, Jirsa et al. 2013; Sporns 2013). In fact, we could show that structural integrity of the MTL and DMN could not predict episodic memory capacity; however, structural integrity could predict functional connectivity changes which in turn were associated with this cognitive capacity. A formal mediation analysis confirmed this relationship. However, the extent to which the anatomical connectome of the human brain can predict functional connectivity at any given moment and relate this to the current cognitive state remains to be seen. The findings presented in this thesis and other studies (McIntosh, Rajah et al. 2003; Deco, Jirsa et al. 2009) suggest that
functional connectivity patterns at any given moment in time are a composition of the underlying anatomical integrity and current cognitive demands responding to changing stimuli in the environment.
8 Limitations and Future Directions
The data presented here raise several new and interesting research questions. As with the general discussion, I will follow the three main themes of this thesis: hippocampal-neocortical network disruptions in patients with mTLE, hippocampal-neocortical networks underlying episodic memory and networks of the brain.

8.1 Predicting Memory Outcome at an Individual Level

The first study of this thesis suggests that fMRI resting state connectivity might be used as an accurate predictor of postsurgical memory decline in patients with mTLE. However, these measures are currently based on group correlations, therefore making it difficult to predict postsurgical memory decline for the individual. In the second study, the pre-specified ROIs would potentially allow for network assessments in new patients as one can derive strength for each of these connections and potentially calculate brain scores for new coming patients (similar to a factor analysis). The advantage of these brain scores is that they hold information about the entire network integrity and not only the strength of one or a few connections. Others and especially graph theory measures attempt to capture the integrity of neuronal networks in single or a few indices (Bullmore and Sporns 2009; Dosenbach, Nardos et al. 2010). However, further research is needed to carefully assess whether these network measures can be used clinically to predict postsurgical memory outcome. For example, I would expect that the pattern of DMN connectivity associated with better episodic memory capacity also indicates greater postsurgical memory decline since patients expressing that pattern rely on an integrated MTL system.

Another drawback of the first two studies of this thesis is that the networks used were specified based on configurations in healthy individuals. However, patients participating in these studies suffered already from recurrent epileptic seizures on average for more than 15 years and as outlined previously neuronal re-organization impacting cognitive functions, such as AM retrieval occurs within and outside the affected MTL in these patients (Bell, Lin et al. 2011; Protzner and McAndrews 2011). Therefore, changes in neuronal networks and especially re-organizations that support behavior might be unique to each patient. Future research is needed to examine re-
organizations of neuronal network underlying episodic memory in individual patients with mTLE and second, to use these network changes to predict postsurgical memory capacity in these individuals. In sum, whereas our results are encouraging in that functional connectivity might be indeed an accurate predictor of postsurgical memory outcome, further research is necessary to assess its predictive value on an individual level.

8.2 Predictive Power of Resting State fMRI in Comparison to Task-Based fMRI

We showed that resting state fMRI functional connectivity between the PCC and hippocampus was strongly associated with episodic memory capacity and indicative of presurgical memory performance and postsurgical memory change. These findings are especially intriguing as clinical episodic memory capacity was sometimes measured months apart from the actual scanning session, therefore relating functional connectivity strength to behavior not closely related in time. An open question remains whether this connection would equally predict behavior performed during scanning. For example, AM retrieval has been shown to engage the connection between the PCC and hippocampus (Sheldon and Levine 2013). It would be interesting to examine whether this connection during AM retrieval would predict successful AM retrieval (maybe in terms of detail richness). Clinically, it would further be interesting to know whether resting state fMRI or task-based fMRI are better predictors of clinical memory measures. For example, it might be that resting state scans reveal the somewhat “typical” connectivity strength for patients with mTLE, in that some patients show low and some stronger connectivity values. During the attempt to retrieve specific AMs, this connectivity might be equally engaged in all patients with mTLE, leading to a small range of variability in connectivity values. Therefore, a reasonable expectation would be that functional connectivity between the PCC and hippocampus derived from resting state fMRI might in fact be a better predictor of postsurgical memory outcome than connectivity values derived from task-based fMRI, such as active AM retrieval (see (McAndrews In Press) for a similar hypothesis).
8.3 Autobiographical Memory Retrieval in Patients with mTLE

Interestingly, patients with mTLE have difficulties in retrieving AM details no matter whether the epileptogenic focus is in the left or right MTL (Viskontas, McAndrews et al. 2000; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011). This lack of episodic details in the AM retrieval process points towards an impairment during AM elaboration in patients with mTLE. Further, two neuroimaging studies examining AM retrieval in this patient population focused on pre-selected AMs, suggesting that demands on construction were minimized during scanning (Addis, Moscovitch et al. 2007; St-Laurent 2012). Both of these studies showed reduced MTL activation and Addis et al. (Addis, Moscovitch et al. 2007) showed connectivity alterations that are in agreement with the data presented here in that the hippocampal system was disengaged during AM retrieval. We extend these findings with our follow-up study in patients with left mTLE that revealed inter- and intrahippocampal connectivity did not change between AM construction and elaboration. Therefore, our data suggest that even though the structural damage in mTLE might be unilateral, both MTLs are disconnected from the AM retrieval network. In this regard, our data suggest that these patients rely on extra-MTL networks to retrieve general AMs, at both construction and elaboration stages.

In future experiments, it would be interesting to aim to dissociate the construction and elaboration processes behaviorally to gain further insight into differences between mTLE patients and controls, especially focusing on the construction phase. For example, it might be that patients with mTLE scroll through their personal semantic knowledge to select the most self-relevant event that matches the retrieval cue, for example the last wedding party. On the other hand, the same retrieval cue in healthy controls might bring online an associative structure of a typical event, for example a typical party with friends which then triggers the retrieval of a specific life event, for example the specific get-together to celebrate somebody’s birthday last summer. Presumably, careful examination of AM interviews (Levine, Svoboda et al. 2002) and introspective reports by patients with mTLE and controls would allow some insight into these construction processes. Further, during elaboration, healthy controls retrieve episodic elements
of this AM while their hippocampi are connected to visual-perceptual areas, whereas patients with mTLE might retrieve the general story line or gist of the event or general visual-perceptual features, such as a general appearance of a wedding dress. In patients with mTLE, the vmPFC might be connected to semantic brain structures throughout AM retrieval supporting general memory organization or directly to visual-perceptual areas during AM elaboration supporting the retrieval of general visual features of AMs. While our current data do not allow teasing apart both AM stages behaviorally, it would be interesting to examine vmPFC connectivity during construction and elaboration processes in patients with mTLE. From this perspective, it is interesting to notice that in our data, worse episodic memory was associated with strong vmPFC connectivity to the LTC and TempP during resting state (see Chapter 4). A possible future research question would be whether this anterior-posterior DMN connectivity pattern would also be associated with better semantic memory scores.

### 8.4 Spatiotemporal Functional Connectivity in Patients with mTLE

The results of the fourth study suggest that the flexible inter- and intrahippocampal connectivity during AM retrieval is restricted in patients with mTLE in comparison to healthy controls. We interpreted these findings such that reduced brain signal variability could potentially have led to this inflexibility. Computational simulations suggest that brain signal variability might be necessary for the neuronal system to explore different network constellations at a shorter time scale (Deco, Jirsa et al. 2011). However, it would be interesting to follow up on these findings and test this proposal in patients with mTLE who show reduced brain signal variability. For example, one could use resting state data ideally with better temporal resolution than fMRI, such as EEG or MEG and calculate transient network configurations. A common approach to assess these network configurations in fMRI is the sliding temporal window correlation, in which the strength of a particular functional connection is calculated for a relatively small temporal window (e.g., 20-30 sec) which is moved in steps through the entire fMRI time series (Kiviniemi, Vire et al. 2011; Jones, Vemuri et al. 2012). This approach allows one to examine how the strength of a particular connection fluctuates over the course of the recording. Based on
the finding that the affected hippocampus showed less brain signal variability than the contralateral hippocampus (Protzner, Valiante et al. 2010) and the findings of computation simulations that brain signal variability predicts exploration of network constellations (Deco, Jirsa et al. 2011), we might expect functional connectivity patterns in patients with mTLE show less exploration into subnetworks in comparison to healthy controls, especially within the affected hemisphere. From this perspective, it is interesting that structural connectivity in patients with mTLE show a more regular, stable topology in graph theoretic terms (Bernhardt, Chen et al. 2011). Nonetheless, whether these graph theoretic findings translate into more stable functional connectivity patterns however, remains to be seen.

8.5 Computational Simulation of MTL Damage

The data shown in this thesis predict very specific patterns of functional connectivity disruption in patients with mTLE. However, as stated above, the patients included in these studies suffered from recurrent seizures for a variable number of years. It would therefore be interesting to examine whether computational simulation projects like the Virtual Brain (http://www.thevirtualbrain.org/tvb/zweif) would reveal similar functional connectivity changes following virtual MTL damage. In fact, on this virtual platform, one could simulate various parameters. First, one could vary the extent of the structural lesion, for example ranging from confined to the hippocampus, incorporating other MTL and lastly LTC. Based on the knowledge that the hippocampus is part of the DMN and rich club (Buckner, Andrews-Hanna et al. 2008; van den Heuvel and Sporns 2011), I would expect that a small lesion to the hippocampus has the same dramatic effects on functional network changes as a larger lesion including LTC. A second obvious parameter to vary is the severity of the lesion, mimicking degrees of MTS and ultimately temporal lobe resections. Studies examining AM retrieval in these patients show that neither the presence/absence of MTS nor pre-/postsurgical status predicts the impairments to retrieve episodic elements (Viskontas, McAndrews et al. 2000; Voltzenlogel, Despres et al. 2006; St-Laurent, Moscovitch et al. 2009). I would therefore expect that these functional connectivity alterations would not change due to varying degrees of lesion severity. Further, simulating the postsurgical stage in which the MTL and LTC are suddenly removed from the model might also
speak to the question whether these connectivity changes abruptly after an acute impact or whether chronic epileptic activity in this region over years is responsible for these changes observed in our data. An extension of this line of research would be to assess what happens to information flow in the brain in the case of MTL damage. As Misic et al. (Misic, Sporns et al. 2014) showed, the MTL appears to be one of the bottlenecks for global communication in the brain. Therefore MTL damage might have a greater impact on this information exchange than damage to other non-critical regions of the brain.

8.6 Neuronal Context of the Hippocampus

We report that the hippocampus coordinates transient networks during AM retrieval in healthy controls. We conclude that the hippocampus might be a neuronal hub supporting episodic memory function. However, it would be interesting to test whether this can be extended to other cognitive domains, such as implicit and short-term memory (Henke, Weber et al. 1999; Henke, Treyer et al. 2003; Olsen, Nichols et al. 2009). A reasonable expectation from the work presented here would be that the hippocampus is connected to a different set of brain region according to different cognitive states. In fact, a neuroimaging study revealed that the hippocampus is connected to different brain regions during learning with and without awareness (McIntosh, Rajah et al. 2003). However, it would be interesting to examine this relationship from the opposite perspective, that is to examine under which experimental conditions the hippocampus is connected, for example, to the vmPFC. Here, activation likelihood estimation (ALE) meta-analysis (www.brainmap.org/ale/) can be used to focus on a specific anatomical region and search for global co-activation patterns across a diverse range of tasks. To extract these co-activation patterns large databases, such as the BrainMap database (www.brainmap.org/), can be used across behavioral tasks and cognitive domains. In addition, a recently developed meta-analysis technique, meta-analytic connectivity modeling (MACM) might help to gain some insight in functional connectivity of maps extracted from ALE meta-analysis (Laird, Eickhoff et al. 2013). For example, a study using this approach on nodes of the DMN demonstrated discrete functional subnetworks, which were associated with affective and perceptual behavior (Laird, Eickhoff et al. 2009). Whereas this analysis sorted studies into pre-
specified cognitive domains given as additional information in BrainMap, one could also use multivariate analysis techniques, such as multidimensional scaling (Torgerson 1958) to identify critical co-activation patterns common to a cluster of behavioral tasks. For example, the vmPFC is always co-activated with the hippocampi during tasks involving the organization of elementary units into one coherent structure. The aim would be to use this meta-analysis as a first step to unravel the neuronal context of the hippocampus, eventually broken into its posterior and anterior elements in both hemispheres. In a second, experimental step, one could then follow up on the results of this meta-analysis and test, using formal network analysis techniques, whether these connections can be experimentally influenced as predicted by the meta-analysis.

In sum, the thesis shows one instance in which the same region in the left anterior hippocampus was functionally connected to different sets of brain regions during different stages of AM retrieval. Future research could extend these finding by systematically investigating the full range of the neuronal context of the hippocampi.
9 Conclusions
As hypothesized, we found that hippocampal-neocortical connectivity indicates episodic memory capacity in patients with mTLE. Further, we provided complementary empirical evidence to computational simulation studies showing that focal structural damage to DMN nodes or rich club members result in widespread alterations in DMN functional connectivity (Alstott, Breakspear et al. 2009; van den Heuvel and Sporns 2011). We extend these findings by demonstrating that these changes are behaviorally meaningful, in that they are associated with individual episodic memory impairment in patients with mTLE. Here, our data supported our original hypothesis that DMN functional connectivity alterations mediated the effect of focal structural damage on episodic memory impairment. We conclude that DMN connectivity, especially the connection between the PCC and hippocampus might be a good candidate to become a clinical marker to predict accurately episodic memory capacity in patients with mTLE.

The second major contribution of this thesis is the further establishment of the hippocampus as the episodic memory hub of the brain, supporting the coordination of transient neocortical networks according to changing cognitive demands. Especially the connections between the hippocampi and posterior regions of the brain, including PCC/RSP and visual-perceptual regions appear critical to fully express the extensive repertoire of episodic memory abilities, such as AM elaboration. Our data further suggest that even unilateral damage to one of the hippocampi disengages the MTL system bilaterally from complex episodic memory tasks, such as AM construction and elaboration. This disengagement might lead to the re-organization of hippocampal-neocortical networks into cortico-cortical networks which might underlie the behavioral deficits seen in patients with mTLE, in that the quality of mental re-experience has changed from vivid detail-rich in healthy controls, to schematic, impoverished AM retrieval in patients with mTLE (Viskontas, McAndrews et al. 2000; Addis, Moscovitch et al. 2007; St-Laurent, Moscovitch et al. 2009; St-Laurent, Moscovitch et al. 2011).

Together, the results of this thesis support the connectionist view of cognition (McIntosh 2000), in that episodic remembering is a result of the transient formation of hippocampal-neocortical networks with each brain region contributing a specific process to the unique moment of re-experience.
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and

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