

Imaging the Functions of Human Hippocampus

Bryan A. Strange

Ph. D. Thesis

*Wellcome Department of Cognitive Neurology,
Institute of Neurology,*

University College London

“Memory frees us from the tyranny of the genes.”

Malcolm Brown. Neuroanatomy lecture, Bristol Medical School, 1995.

I thank Ray Dolan and Karl Friston for their enthusiastic supervision, Rik Henson, Paul Fletcher, Leun Otten and Mick Rugg for their help and advice, and my family and friends for their support and encouragement.

The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without prior written consent of the author.

Since the 1950s it has been known that damage to the hippocampus impairs conscious long-term memory for events and episodes. However, the precise functional role of the hippocampus in episodic memory remains controversial. Hippocampal damage impairs the acquisition of novel episodic memories, which may suggest a role in processing novel stimuli. In this thesis, a series of functional magnetic resonance imaging (fMRI) experiments were conducted to characterise the human hippocampal response to novelty. The results from four experiments suggest a functional dissociation between anterior and posterior hippocampal regions with respect to the relative familiarity of study items. Responses in anterior hippocampus index novelty whereas posterior hippocampal responses index familiarity. Anterior hippocampal responses showed adaptation with repeated presentations of a given stimulus, indicating this region is sensitive to the recency of prior occurrence. Anterior hippocampus was also engaged by stimuli that violated expectation, suggesting that the anterior hippocampal role in processing recency of prior occurrence reflects a more general role in detecting mismatches between expectation and experience. This anterior hippocampal mismatch response may represent an important component of episodic memory encoding. The posterior hippocampal familiarity response may reflect retrieval of familiar stimuli. This functional segregation, within human hippocampus for the processing of relative familiarity, may provide a basis for understanding the memory deficits that arise from damage to different regions of the hippocampus.

Table of Contents

Chapter 1 Introduction

1.1 Anatomy	13
1.2 Discovery of multiple memory systems in the brain	15
1.21 Declarative and nondeclarative memory systems	17
1.3 The Amnesic syndrome	23
1.31 Semantic memory and the hippocampus.....	24
1.32 Critical components of the medial temporal lobe memory system	25
1.33 Hippocampal role in recall vs recognition	29
1.34 Hippocampal role in memory – current consensus	31
1.4 Hippocampal novelty-dependent responses	31
1.41 Behavioural responses to novelty.....	32
1.42 Effects of hippocampal lesions on behavioural responses to novelty	35
1.43 Novelty-sensitive activity of single neurones	37
1.43a Rodents.....	37
1.43b Rodent EEG oscillatory activity.....	40
1.43c Monkey	42
1.43d Human.....	44
1.43e Human local field potentials.....	45
1.44 How other models of hippocampal function may suggest novelty-dependent processes in the hippocampus	47
1.5 Functional imaging as a tool to investigate memory processes of the human hippocampus	54
1.6 Overview of thesis	57

Chapter 2 Materials and Methods

Part I Functional Magnetic Resonance Imaging

2.1 Non-invasive neuroimaging techniques	62
2.2 The physics of NMR and MRI	63
2.21 Spin	63
2.22 Net magnetisation	65
2.23 Radiofrequency magnetic fields.....	65
2.24 Relaxation	67
2.25 Image formation: frequency and phase encoding.....	70
2.26 Voxels	71
2.27 Image contrast.....	72
2.28 Ultrafast MRI sequences: Echo-Planar Imaging	72

2.3 fMRI and the magnetic properties of blood.....	74
2.31 BOLD contrast in fMRI	74
2.32 Neurophysiology and BOLD	75

Part II Statistical Analysis of Functional MRI Time Series

2.4 Introduction.....	78
2.5 Spatial preprocessing.....	79
2.51 Realignment	79
2.51a Spatial.....	79
2.51b Temporal.....	79
2.52 Spatial normalisation.....	80
2.53 Spatial smoothing.....	81
2.6 Characterising haemodynamic responses using the General Linear Model.....	82
2.61 Parameter estimation using the General Linear Model	82
2.62 Statistical inference and the Theory of Gaussian Fields.....	85
2.62a Anatomically constrained hypotheses	85
2.62b Anatomically open hypotheses: levels of inference	86
2.7 Event-related fMRI.....	87
2.8 Optimising experimental design	89
2.9 Inferences about subjects and populations: Random vs Fixed effects analyses	90

Chapter 3 Functional Segregation within Human Hippocampus for

Relative Familiarity

3.1 Introduction:	94
3.2 Materials and methods:	97
3.21 Subjects.....	97
3.22 Psychological task.....	97
3.23 Data acquisition.....	98
3.24 Data analysis	99
3.3 Results:.....	102
3.4 Discussion:	107
3.41 Functional segregation	107
3.42 Temporal dynamics of hippocampal responses.....	113
3.43 Summary	116

Chapter 4 Neuroanatomical Correlates of Rule Learning

4.1 Introduction:	119
4.2 Materials and Methods:	122
4.21 Subjects	122
4.22 Psychological task.....	122
4.23 Data acquisition.....	123
4.24 Data analysis	123
4.3 Results:	128
4.31 Behaviour	128
4.32 Functional imaging	129
4.4 Discussion:	133
4.41 Fronto-polar prefrontal cortex.....	133
4.42 Hippocampus	137
4.43 Summary	140

Chapter 5 Detection of Perceptual, Semantic and Emotional Deviance

Part I Non-Adapting Responses

5.1 Introduction:	143
5.2 Materials and Methods:	146
5.21 Subjects	146
5.22 Psychological task.....	146
5.23 Data acquisition.....	148
5.24 Data analysis	148
5.3 Results:	151
5.31 fMRI data	151
5.32 Behavioural data	158
5.4 Discussion:	160
5.41 Summary	165

Part II Adapting Anterior Hippocampal Responses

5.5 Introduction:	168
5.6 Materials and Methods:	170
5.61 Data analysis	170
5.7 Results:	173
5.8 Discussion:	179

Chapter 6 Human Medial Temporal Activity Predicts Subsequent Memory: Dissociable Perirhinal, Hippocampal and Parahippocampal Roles in Verbal Encoding

6.1 Introduction.....	185
6.2 Materials and Methods.....	188
6.21 Subjects.....	188
6.22 Psychological task.....	188
6.23 Data acquisition.....	189
6.24 Data analysis.....	190
6.24a Subsequent memory event-related analysis of the list body.....	191
6.24b Covariate analysis.....	192
6.24c Primacy analysis.....	192
6.3 Results:.....	194
6.31 Behaviour.....	194
6.32 Functional imaging.....	196
6.4 Discussion:.....	204
6.41 Summary.....	208

Chapter 7 Anatomical and Neuromodulatory Bases for Functional Segregation within the Hippocampus

7.1 Anatomical basis: Connectivity.....	211
7.11 Cortical connections.....	212
7.11a Entorhinal cortex input to hippocampus.....	212
7.11b Cortical inputs to entorhinal cortex.....	213
7.11c Medial temporal cortical inputs to hippocampus.....	217
7.11d Hippocampal cortical efferents.....	218
7.11e Prefrontal cortical inputs to hippocampus.....	218
7.11f Intrahippocampal longitudinal association connections.....	221
7.12 Subcortical connections.....	222
7.13 Anterior hippocampus and the autonomic system.....	222
7.14 Anterior hippocampus and amygdala.....	224
7.2 Neuromodulatory projections.....	225
7.3 Functional segregation for spatial learning.....	226
7.4 Conclusion.....	231

Chapter 8 General Discussion

8.1 Anterior hippocampus	233
8.11 Mismatch detection	233
8.12 The origin of hippocampal response adaptation.....	235
8.13 Evidence against anterior hippocampal role in mismatch detection	236
8.14 Anterior hippocampus and encoding.....	242
8.15 Implications for a mismatch detection role	244
8.2 Posterior hippocampus	245
8.3 Control considerations.....	246
8.31 Eye movements	246
8.32 Attention	248
8.33 Task control	249
8.4 The hippocampus as part of a distributed limbic-neocortical novelty detection network	252
8.5 Conclusion	253

References

Table of Figures

Chapter 1

Figure 1.1. Classification of long-term memory.....22

Chapter 2

Figure 2.1 Spin and precession of a single proton.....64

Chapter 3

Figure 3.1. The introduction of perceptual and exemplar novelty in the context of item learning.....101

Figure 3.2. Hippocampal region in which there is a significant time by condition interaction in response to perceptual novelty reflecting adaptation with familiarity.....104

Figure 3.3. Dissociation in the anterior-posterior hippocampal axis for exemplar novelty.....106

Figure 3.4. Topography of hippocampal activation as a function of relative familiarity...113

Chapter 4

Figure 4.1. Experimental design and behavioural performance.....127

Figure 4.2. Main effect of rule change.....131

Figure 4.3. Left anterior hippocampus responds to exemplar change.....132

Chapter 5

Figure 5.1. Examples of presented nouns.....145

Figure 5.2. Areas commonly activated by all oddball types.....153

Figure 5.3. The right prefrontal cortex exerts significant modulatory effects on activity in the right inferior parietal lobule during presentation of all oddball types relative to control nouns.....154

Figure 5.4. Attribute-specific activations.....157

Figure 5.5. Recall performance for the 10 subjects who completed the psychological task outside of scanning, recalling nouns freely after each 19 noun list presentation.....159

Figure 5.6. Left anterior hippocampus is activated by the initial occurrence of all oddball types and this response adapts over the experiment.....174

Figure 5.7: The adapting antero-lateral hippocampal response to semantic oddballs is significantly modulated by depth of encoding.....176

Figure 5.8: Non-adapting responses to oddballs.....177

Chapter 6

Figure 6.1 Experimental set-up and behavioural results.....195

Figure 6.2 Medial temporal encoding-related activation predictive of subsequent memory.....198

Figure 6.3 Mean encoding-related activation.....200

Figure 6.4 Neuronal correlates of the primacy effect.....203

Chapter 7

Figure 7.1. Schematic diagram of monkey parahippocampal (PHG) and perirhinal (PRH) connections with entorhinal cortex (EC) and EC-dentate gyrus (DG) connections.....215

Figure 7.2 Topographical organisation of the connections between temporal cortex and CA1 of the macaque hippocampus.....216