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WASHINGTON UNIVERSITY IN ST. LOUIS

School of Engineering and Applied Science Department of Biomedical Engineering

Dissertation Examination Committee: Eric C. Leuthardt, Chair Maurizio Corbetta, Co-Chair Mark Anastasio Dennis L. Barbour Marcus E. Raichle Abraham Z. Snyder

The Electrophysiology of Resting State fMRI Networks Carl D. Hacker

> A dissertation presented to The Graduate School of Washington University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

> > May 2017

St. Louis, Missouri

Table of Contents

Table of Figures	vi
Table of Tables	viii
Acknowledgements	ix
Abstract of the Dissertation	xi
Chapter 1: General Introduction and Background	1
1.1 Spontaneous Activity: A Paradigm Shift in Systems Neuroscience	1
1.2 The functional role of spontaneous activity in health and disease	2
1.3 Spontaneous electrophysiological activity and relation to resting state fMRI	4
1.4 Technical challenges in relating invasive electrophysiology to resting state networks	6
1.4.1 ECoG:fMRI Coregistration	6
1.4.2 Defining fMRI Resting State Networks in Individual Subjects	7
1.5 Summary	8
1.6 Organization of the Dissertation	9
1.6 References	10
Chapter 2: Co-registration of Electrocorticography with Functional Magnetic Resonance Imag	ging
	14
2.1 Introduction	14
2.2 CT to Structural MRI Registration	14
2.3 Electrode Segmentation	16
2.4 Deformation Correction	19
2.5 Surface to Electrode Sampling	20
2.5 fMRI Distortion Correction	21
2.6 Summary	22
Chapter 3: Resting State Network Estimation in Individual Subjects	26
3.1 Introduction	27
3.2 Methods	31
3.2.1 Participants	31
3.2.2 Neuroimaging methods	32
3.2.3 Meta-analysis of task fMRI and generation of training data	35
3.2.4 MLP design	37
3.2.5 Application of method to individuals	40
3.2.6 Comparison of the MLP to linear discriminant analysis and dual regression	42
3.3 Results	44
3.3.1 MLP training	44
3.3.2 MLP performance in the Validation datasets	46
3.3.3 Comparison of the MLP to alternative RSN estimation schemes	51

3.4.1 Inter-individual variability of MLP outputs 56 3.4.2 External Validity and Generalizability 59 3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analysis (LDA) 61 3.4.4 Dynamics of perceptron training reflect hierarchical brain organization 63 3.4.5 MLP performance applied to the evaluation of fMRI methodology 64 3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References. 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 88 Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping. 104 4.3 Results 103 4.3 Results in Tumor Patients 111 1.4 Discussio	3.4 Discussion	
3.4.2 External Validity and Generalizability 59 3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analysis (LDA) 61 3.4.4 Dynamics of perceptron training reflect hierarchical brain organization 63 3.4.5 MLP performance applied to the evaluation of fMRI methodology. 64 3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References 69 Appendix 3.0: Multi-layer Perceptron Training Algorithm 74 Appendix 3.1: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 84 Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 4.4 Discussion 120 Chapter 5: ECoG Local	3.4.1 Inter-individual variability of MLP outputs	
3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analysis (LDA) 61 3.4.4 Dynamics of perceptron training reflect hierarchical brain organization. 63 3.4.5 MLP performance applied to the evaluation of fMRI methodology. 64 3.4.5 Limitations 66 3.4.7 Summary 68 3.5 References. 69 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 93 Resting State fMRI. 93 4.1 Introduction. 94 4.2 Methods. 97 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State fMRI 127 5.1 Introduction. 128 5.2.1 Image Acuisition and RSN Definition <	3.4.2 External Validity and Generalizability	59
61 3.4.4 Dynamics of perceptron training reflect hierarchical brain organization. 63 3.4.5 MLP performance applied to the evaluation of fMRI methodology. 64 3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References. 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm. 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 83 Resting State fMRI. 93 4.1 Introduction 94 4.2 Methods. 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping. 104 4.3 Results 105 4.3.1 ROC Analysis. 108 4.3 Results in Tumor Patients 111 4.4 Discussion 113 4.5 References 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State <td>3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analy</td> <td>sis (LDA)</td>	3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analy	sis (LDA)
3.4.4 Dynamics of perceptron training reflect hierarchical brain organization 63 3.4.5 MLP performance applied to the evaluation of fMRI methodology 64 3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.3.1 ROC Analysis 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 4.4 Discussion 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State fMRI 127 5.1 Introduction 128 5.2.1 Subjects and Coverage		61
3.4.5 MLP performance applied to the evaluation of fMRI methodology 64 3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 tMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 4.4 Discussion 127 5.2 Methods 128 5.2.1 Imroduction 127 5.2 Methods 128 5.2.1 Imroduction and RSN Definition 128 5.2.2 Subjects and Coverage	3.4.4 Dynamics of perceptron training reflect hierarchical brain organization	63
3.4.6 Limitations 66 3.4.7 Summary 68 3.5 References 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 14 Discussion 113 4.5 References 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State TMRI 127 5.1 Introduction 127 5.2 Methods 128 5.2.1 I	3.4.5 MLP performance applied to the evaluation of fMRI methodology	64
3.4.7 Summary 68 3.5 References 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 83 Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 1.4 Discussion 113 4.5 References 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State fMRI 128 5.2.1 Image Acuisition and RSN Definition 128 5.2.2 Subjects and Coverage 129 5.2.3 ECoG Proces	3.4.6 Limitations	66
3.5 References 69 Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 93 Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3.3 Results in Tumor Patients 111 4.4 Discussion 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State fMRI 127 5.1 Introduction 127 5.2 Methods 128 5.2.1 Image Acuisition and RSN Definition 128 5.2.2 Subjects and Coverage 129 5.2.3 ECoG Proce	3.4.7 Summary	
Appendix 3.A: Multi-layer Perceptron Training Algorithm 74 Appendix 3.B: Algebraic Comparison of Methods 79 3.6 Supplemental Materials 84 Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using 83 Resting State fMRI 93 4.1 Introduction 94 4.2 Methods 97 4.2.1 Subjects 97 4.2.2 fMRI Analysis 98 4.2.3 Electrode MRI Coregistration 101 4.2.4 Electrocortical Stimulation Mapping 102 4.2.5 Comparison of fMRI Analysis and ECS Mapping 104 4.3 Results 105 4.3.1 ROC Analysis 108 4.3.2 Minimization of False Negatives 109 4.3 Results in Tumor Patients 111 4.4 Discussion 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State 120 Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State 127 5.1 Introduction 128 5.2.1 Image Acuisition and RSN Definition 128 5.2.2 Subjects and Coverage 129 5.2.3 ECoG Processing 131	3.5 References	69
Appendix 3.B: Algebraic Comparison of Methods793.6 Supplemental Materials84Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex UsingResting State fMRI934.1 Introduction944.2 Methods974.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	Appendix 3.A: Multi-layer Perceptron Training Algorithm	74
3.6 Supplemental Materials84Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex UsingResting State fMRI.934.1 Introduction944.2 Methods974.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	Appendix 3.B: Algebraic Comparison of Methods	79
Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex UsingResting State fMRI	3.6 Supplemental Materials	
Resting State fMRI934.1 Introduction944.2 Methods974.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Corte	ex Using
4.1 Introduction944.2 Methods974.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	Resting State fMRI	
4.2 Methods974.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StateFMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.3 Results1355.3 Results135	4.1 Introduction	
4.2.1 Subjects974.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2 Methods	
4.2.2 fMRI Analysis984.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2.1 Subjects	
4.2.3 Electrode MRI Coregistration1014.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StateFMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2.2 fMRI Analysis	
4.2.4 Electrocortical Stimulation Mapping1024.2.5 Comparison of fMRI Analysis and ECS Mapping.1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2.3 Electrode MRI Coregistration	
4.2.5 Comparison of fMRI Analysis and ECS Mapping.1044.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2.4 Electrocortical Stimulation Mapping	
4.3 Results1054.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.2.5 Comparison of fMRI Analysis and ECS Mapping	
4.3.1 ROC Analysis1084.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1335.3 Results135	4.3 Results	
4.3.2 Minimization of False Negatives1094.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.3.1 ROC Analysis	
4.3.3 Results in Tumor Patients1114.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.3.2 Minimization of False Negatives	
4.4 Discussion1134.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State127fMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.3.3 Results in Tumor Patients	
4.5 References120Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State127fMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.4 Discussion	
Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting StatefMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	4.5 References	
fMRI1275.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting	g State
5.1 Introduction1275.2 Methods1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	fMRI	
5.2 Methods.1285.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	5.1 Introduction	
5.2.1 Image Acuisition and RSN Definition1285.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	5.2 Methods	
5.2.2 Subjects and Coverage1295.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	5.2.1 Image Acuisition and RSN Definition	
5.2.3 ECoG Processing1315.2.4 Correlation vs. Distance Trend Removal1315.2.5 ECoG:fMRI Comparison Methodology1335.3 Results135	5.2.2 Subjects and Coverage	
5.2.4 Correlation vs. Distance Trend Removal.1315.2.5 ECoG:fMRI Comparison Methodology.1335.3 Results.135	5.2.3 ECoG Processing	
5.2.5 ECoG:fMRI Comparison Methodology	5.2.4 Correlation vs. Distance Trend Removal	
5.3 Results	5.2.5 ECoG:fMRI Comparison Methodology	
	5.3 Results	

5.3.1 Within- versus Across-RSN Comparison	. 135
5.3.2 Spatial Correspondence of ECoG and fMRI Correlations	. 137
5.4 Discussion	. 143
5.4.1 Slow Cortical Potential Correlations Within Resting State Networks	. 143
5.4.2 ECoG:fMRI Correspondence Across LFP and BLP Frequencies	. 143
5.4.3 The Frequency Dead Zone	. 144
5.4.4 Spectral Variability in ECoG:fMRI Correspondence	. 146
5.5 References	. 147
Chapter 6: Resting state electrophysiology links classic brain rhythms with hierarchical function	nal
systems	. 149
Abstract	. 149
6.1 Introduction	. 150
6.2 Methods	. 152
6.2.1 Participants	. 152
6.2.2 Image Acquisition and Preprocessing	. 153
6.2.3 ECoG Data Acquisition and Preprocessing	. 155
6.2.4 BOLD-ECoG Comparison Methodology	. 156
6.3 Results	. 158
6.4 Discussion	. 167
6.4.1 Frequency specificity of fMRI RSNs	. 167
6.4.2 Intrinsic electrophysiological activity differentiates the intrinsic vs. extrinsic systems	168
6.4.3 Relation to BOLD fMRI Frequencies	. 169
6.4.4 Cross-frequency Coupling	. 170
6.4.5 Methodological Considerations	. 171
6.4.6 Conclusion	. 172
6.5 References	. 173
Chapter 7: Relationship Between Resting State Correlations and Task-Induced Activity	. 177
7.1 Introduction	. 177
7.2 Methods	. 180
7.2.1 Patients	. 180
7.2.2 Resting State Analyses	. 180
7.2.3 Task Design	. 180
Reaching Task Design:	. 180
7.2.3.2 Auditory Task Design	. 182
7.3 Results	. 184
7.3.1 Power changes during task performance	. 184
7.3.2 Relation of Task Performance to Resting State Correlations	. 186
7.4 Discussion	. 190

7.4.1 Spatial and Spectral Distribution of Task Responses
7.4.2 Correspondence Between Resting State Correspondence and Task-Induced Activity 191
7.4.3 Spectral Specificity and Magnitude Scaling in Task Responses vs. Resting Correlations
7.4.4 Implications for the Interpretation of Large-Scale Correlations of Spontaneous Activity
7.5 References
Chapter 8: Concluding Remarks 197

Table of Figures

Figure 2.1. ECoG coregistration methodology.	15
Figure 2.2. Electrode selection and sorting	18
Figure 2.3. Projection of electrodes to cortical surface.	19
Figure 2.4. Precision Electrode-to-Surface Registration	21
Figure 2.6 Registration of Electrodes to EPI Data	24
Figure 2.7. Assignment of RSN membership to electrodes	25
Figure 3.1. Seed ROIs for Generation of Correlation Map Data.	37
Figure 3.2. Single-subject, Voxel-wise Estimation of RSNs Using the Trained MLP	41
Figure 3.3. Projection of RSNs into PCA space.	44
Figure 3.4. MLP Training Trajectories as Reflected in the Optimization Dataset	45
Figure 3.5. RSN Topographies in Individual Participants from Validation Dataset	47
Figure 3.6. MLP SMN Results Obtained in Validation Dataset 2 Individuals	48
Figure 3.7. Surface-averaged MLP Results.	49
Figure 3.8. Volume-averaged MLP Results.	50
Figure 3.9. Comparison of MLP to Alternative Methodologies	53
Figure 3.10. Examples of Objective Evaluation of Methodology.	64
Figure 3.A1. Standard Multi-layer Perceptron Architecture.	76
Figure 3.A2. Learning rate (η) dependence on iteration index	77
Figure 3.A3. MLP Output Values over the Course of Training.	78
Figure 3.S1. ROIs in Volume Space	87
Figure 3.S2. Search Space for Optimal Perceptron Architecture.	89
Figure 3.S3. Inter-subject Variability - Functional vs. Structural	90
Figure 4.1. Voxel-wise classification of resting state networks (RSNs) using the multilayer	
perceptron (MLP) algorithm	99
Figure 4.2. Schematic for classifying electrodes as motor or language positive using resting	state
fMRI and the gold standard electrocortical stimulation (ECS) in epileptic patients	103
Figure 4.3. RSN maps produced by the multilayer perceptron (MLP) algorithm for the six	
epilepsy patients in the study	106
Figure 4.4. Visualization of the results for motor and language cortex using both ECS and t	he
mulitlayer perceptron (MLP) in the six epilepsy patients	107
Figure 4.5. ROC curves for epilepsy patients comparing motor and language electrode	
identification by the multilayer perceptron (MLP) algorithm to the gold standard ECS	108
Figure 4.6. The method employed to define a "no-cut" area in epilepsy patients, in which the	ne
probability of damage to motor cortex is substantial	110

Figure 4.7. RSN maps produced by the multilayer perceptron (MLP) algorithm for six tumor	•
patients in the study.	. 112
Figure 4.8. Visualization of the results for identifying eloquent cortex using both ECS and th	e
mulitlayer perceptron (MLP) in two tumor patients.	. 113
Figure 5.1. ECoG Data and RSN Coverage	. 130
Figure 5.2. Pair-wise temporal fMRI correlations across ECoG electrodes	. 133
Figure 5.3. Pair-wise Temporal ECoG Correlations	. 133
Figure 5.4 Exemplar: Within- versus Across-RSN ECoG Correlations.	. 135
Figure 5.5. Within- versus Across-RSN Comparison: Groups Results	. 136
Figure 5.6. Spatial correspondence of fMRI and ECoG LFP correlation maps	. 137
Figure 5.7. Spatial correspondence of fMRI and ECoG BLP correlation maps	. 138
Figure 5.8. fMRI:ECoG Spatial Correspondence: Group Results	. 139
Figure 5.9. Interfrequency spatial similarity of ECoG correlation maps	. 140
Figure 5.10. ECoG:BOLD Corresopndence and Intrinsic ECoG Dimensionality	. 142
Figure 6.1. Spatial correspondence of ECoG and fMRI correlation maps in a single subject	. 160
Figure 6.2. ECoG:fMRI correspondence spectra vary according to RSN	. 162
Figure 6.3. Average ECoG:fMRI Correspondence Spectra	. 164
Figure 6.4. System-level spectral specificity of ECoG correlations	. 166
Figure 7.1. Time-Frequency Analysis of ECoG Activity in 3D Reach Task	. 185
Figure 7.2. Comparison of Task Related ECoG Activity across Tasks	. 186
Figure 7.3. Task:Rest Spatial Correspondence Methodology	. 188
Figure 7.4 Spectral Correspondence of Task Activity and Task:Rest Correspondence	. 189
Figure 7.5 Magnitude Scaling of Resting State Correlations and Task Activity	. 190

Table of Tables

Table 3.1. Characteristics of the Training, Test and Validation datasets	
Table 3.2. Studies of functional co-activation used to generate seed ROIs	
Table 3.3. RSN classification (AUC) and estimation (RMS) performance	
Table 3.4. RSN classification performance for alternative methodologies	
Table 4.1: Demographic and clinical information for seizure patients	125
Table 4.2: Demographic and clinical information for tumor patients	126
Table 6.1. Patient characteristics and experimental data.	

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Abstract of the Dissertation

The Electrophysiology of Resting State fMRI Networks

by

Carl David Hacker

Doctor of Philosophy in Biomedical Engineering Washington University in St. Louis, 2017 Dr. Eric C. Leuthardt, Chairperson

Traditional research in neuroscience has studied the topography of specific brain functions largely by presenting stimuli or imposing tasks and measuring evoked brain activity. This paradigm has dominated neuroscience for 50 years. Recently, investigations of brain activity in the resting state, most frequently using functional magnetic resonance imaging (fMRI), have revealed spontaneous correlations within widely distributed brain regions known as resting state networks (RSNs). Variability in RSNs across individuals has found to systematically relate to numerous diseases as well as differences in cognitive performance within specific domains. However, the relationship between spontaneous fMRI activity and the underlying neurophysiology is not well understood. This thesis aims to combine invasive electrophysiology and resting state fMRI in human subjects to better understand the nature of spontaneous brain activity. First, we establish an approach to precisely coregister intra-cranial electrodes to fMRI data (Chapter 2). We then created a novel machine learning approach to define resting state networks in individual subjects (Chapter 3). This approach is validated with cortical stimulation in clinical electrocorticography

(ECoG) patients (Chapter 4). Spontaneous ECoG data are then analyzed with respect to fMRI time-series and fMRI-defined RSNs in order to illustrate novel ECoG correlates of fMRI for both local field potentials and band-limited power (BLP) envelopes (Chapter 5). In Chapter 6, we show that the spectral specificity of these resting state ECoG correlates link classic brain rhythms with large-scale functional domains. Finally, in Chapter 7 we show that the frequencies and topographies of spontaneous ECoG correlations specifically recapitulate the spectral and spatial structure of task responses within individual subjects.

Chapter 1: General Introduction and Background

1.1 Spontaneous Activity: A Paradigm Shift in Systems Neuroscience

Before the 1990's, spontaneously correlated resting-state networks with spatially focal nodes were not suspected to exist. However, focality of brain function has long been known; as early as the 1860's, Paul Broca discovered that damage to a specific location in the left frontal lobe produced a specific aphasia (Broca, 1861). Other early but significant discoveries included posterior localization of language function (Wernicke, 1876) and electrical stimulation mapping of motor cortex (Fritsch, Hitzig, 1870). By the time Korbinian Brodmann divided the cortex into 52 regions based on cytoarchitectonic features (Brodmann, 1909) converging evidence supported the localization of function in particular brain areas. Electrical stimulation studies of Wilder Penfield (1937) and George Ojemann (1983) have conclusively showed specific localization of language and motor function in human subjects.

Traditional research in neuroscience has studied the topography of specific brain functions largely by presenting stimuli or imposing tasks and measuring evoked brain activity. This paradigm has dominated neuroscience for 50 years. Endogenous activity has been treated as noise and removed through averaging (Engel et al., 2001, Varela et al., 2001, Schroeder and Lakatos, 2009, Raichle, 2010). Investigations of ongoing brain activity in the resting state (in the absence of salient sensory and motor events) have revealed spontaneous correlations within widely distributed brain regions; most of these observations have come from functional magnetic resonance imaging (fMRI) (Biswal et al., 1995, Fox et al., 2005).

Biswal and colleagues first described resting state functional magnetic resonance imaging

(fMRI) in 1995 (Biswal et al., 1995). The literature in this field has since been growing exponentially (Snyder and Raichle, 2012). Most of this work has been directed towards describing the statistical properties of intrinsic blood oxygenation level dependent (BOLD) signal fluctuations in health and disease (Biswal et al., 2010, Fox and Greicius, 2010, Zhang and Raichle, 2010). Spontaneous BOLD activity recapitulates, in the topographies of its temporal covariance structure, task-based fMRI responses to a wide variety of behavioral paradigms (Smith et al., 2009). These topographies currently are known as resting state networks (RSNs) or, equivalently, intrinsic connectivity networks (ICNs). RSNs have now been mapped over virtually all of the cerebral cortex as well as many subcortical structures including the cerebellum (Buckner et al., 2011, Power et al., 2011, Yeo et al., 2011, Choi et al., 2012, Lee et al., 2012).

1.2 The functional role of spontaneous activity in health and disease

The physiological functions of resting state activity are under active investigation. The topographies of RSNs recapitulate BOLD responses evoked by performance of sensory, motor, and cognitive tasks (Smith et al., 2009). RSNs can be modified by intensive training (Albert et al., 2009, Lewis et al., 2009), and are predictive of future performance on novel tasks (Baldassarre et al., 2012). Some evidence exists that spontaneous activity plays an active role in online processing, predicting perceptions (Sadaghiani et al., 2010), or serving as a substrate of short term memory (Sauseng et al., 2009). Resting state activity may also represent offline processes that maintain the functional integrity of the brain through synaptic homeostasis (Pizoli et al., 2011), or by supporting episodic memory consolidation (Tambini et al., 2010). RSNs are known to be altered in several

mental health disorders, e.g. schizophrenia (Calhoun et al., 2009), major depression (Greicius et al., 2007), and autism (Anderson et al., 2011).

One of the major benefits of resting-state functional connectivity as means of assessing the status of functional systems in disease is that it avoids the interpretive confound of variable task performance (Fox and Greicius, 2010, Zhang and Raichle, 2010). This 'chicken versus egg' ambiguity confounds all task-based neuroimaging studies of functional deficits: does a change in regional brain function associated with an abnormally performed task reflect dysfunction of that brain region, or does it reflect the altered performance of the task? As a particularly vexing example, motor tasks elicit reduced responses in supplementary motor area in akinetic patients with Parkinson's disease (Grafton, 2004), but does this reflect impaired task performance, or do the reduced responses directly reflect supplementary motor area dysfunction? In other cases, compliance with task paradigms may simply be impossible due to neurologic deficits or confusion.

In application to Alzheimer's disease, numerous resting-state functional connectivity functional MRI studies have demonstrated reduced functional connectivity primarily within the default mode network (Mevel et al., 2011). This result is concordant with the known distribution of Alzheimer's disease histopathology (Buckner et al., 2005, Nelson et al., 2009, Shin et al., 2011). Moreover, default mode network functionality is central to episodic memory (Buckner et al., 2008), which is precisely the cognitive domain that characteristically is impaired in Alzheimer's disease. Thus, in Alzheimer's disease, the locus of greatest pathology, the characteristic cognitive deficit and the topography of the most prominent resting-state functional connectivity functional MRI abnormalities all coincide.

3

In some cases, resting state fMRI studies have led to new insights into disease pathogenesis. Classical accounts of the pathophysiology of Parkinson's disease have emphasized degeneration of dopaminergic nigrostriatal neurons with consequent dysfunction of cortico– striatal–thalamic loops. In contrast, post-mortem studies indicate that pathological changes in Parkinson's disease (Lewy neurites and Lewy bodies) first appear primarily in the lower brainstem with subsequent progression to more rostral parts of the neuraxis. In advanced Parkinson subjects, we found that striatal functional connectivity with the brainstem was markedly reduced, reinforcing the importance of this structure in the pathophysiology of Parkinson's disease (Hacker et al., 2012). Interestingly brainstem-striatal connectivity was graded (posterior putamen > anterior putamen > caudate), in both patients with Parkinson's disease and control subjects, in a manner that corresponds to well-documented gradient of striatal dopaminergic function loss in Parkinson's disease. We hypothesized that this gradient provides a clue to the pathogenesis of Parkinson's disease, with the spread of pathology following the distribution of functional connectivity as measured by resting state fMRI.

1.3 Spontaneous electrophysiological activity and relation to resting state fMRI

Most of the understanding of the neural basis of BOLD has been obtained through the combination of electrophysiology and fMRI in the context of sensory stimuli or motor responses. Task-evoked BOLD responses correspond better to local field potentials (LFPs, i.e. dendritic currents that reflect the input to a neural population; (Mitzdorf, 1985)) than single unit discharge (Logothetis et al., 2001). Band-limited power (BLP, or equivalently, the squared amplitude envelope, Fig 1) of gamma frequency LFPs exhibits the strongest correlation with evoked BOLD

responses, but activity at all frequencies is significantly correlated (Goense and Logothetis, 2008). In humans, evoked gamma spatially corresponds to BOLD responses (Brovelli et al., 2005). Evoked decreases in gamma power show similar correspondence in the human default mode network (Miller et al., 2009) and monkey visual cortex (Shmuel et al., 2006). Correspondence between evoked BLP and BOLD motivates the hypothesis that spontaneous BLP correlations correspond to BOLD RSNs (**Aim 2**).

Less progress has been made in defining the electrophysiologic correlates of spontaneous BOLD fluctuations. (Goldman et al., 2002) and (Laufs et al., 2003a) described BOLD correlates of EEG power fluctuations, but with low specificity with respect to the recording electrode location (Laufs et al., 2003b). Mantini et al. (2007) found spectral specificity in the correlations of EEG power to BOLD RSNs. De Pasquale et al. (2010) and Brookes et al. (2011) reported correlated beta frequency BLP fluctuations corresponding to BOLD RSNs using MEG. The MEG emphasis on beta frequencies does not correspond well to results obtained by invasive means (e.g. Brovelli et al., 2005), which characteristically emphasize gamma frequencies. The spatial resolution of MEG is in the multiple centimeter range (Hauk et al., 2011). EEG is even more limited spatially and unreliable in the gamma frequency range (Yuval-Greenberg et al., 2008).

Invasive electrophysiologic studies are necessary to overcome these limitations, but few have been performed. Raw LFPs at high frequencies are only correlated on a scale of millimeters; in contrast, low frequency LFPs and slow fluctuations in BLP can be correlated over longer distances (Leopold et al., 2003). The most prominent property of spontaneous BOLD fluctuations is inter-hemispheric correlation (Achard et al., 2006). Gamma BLP fluctuations are correlated across hemispheres at rest (Shmuel et al., 2006, Nir et al., 2008). The single extant study comparing LFP phase coherence to RSNs found that the slow cortical potentials (SCP < 0.5 Hz) are the best correlate in the motor system (He et al., 2008). A relationship between gamma BLP correlations and BOLD RSN topography was reported, but not during slow wave sleep (SCP correlations remained significant in all states). SCP correlation patterns persist under anesthesia (Breshears et al., 2010).

1.4 Technical challenges in relating invasive electrophysiology to resting state networks

1.4.1 ECoG:fMRI Coregistration

A primary objective of this work is to relate spontaneous electrophysiology as measured by ECoG to the anatomy of systems in the brain and their corresponding funcitons. Specifically, electrophysiologic results are to be compared to functional connectivity defined by fMRI, about which our knowledge is largely based on topography, or the spatial distribution of correlations. Therefore, precise alignment across modalities is necessary to study the electrophysiology of fMRI correlations and their organization into resting state networks. However, ECoG:fMRI coregistration presents an array of technical challenges.

MR imaging of subjects with electrode grids in place is currently considered too great a risk to patients, requiring post-implant computed x-ray tomography (CT) scans for electrode localization. This neccesitates accurate CT-MRI coregistration and methodology to extract electrode coordinates from the registered CT. However, anatomical distortion of brain geometry post grid insertion results in a displacement of the CT-derived electrode coordinates relative to the MR-derived pial surface. This problem required the development of sophisticated

methodology to precisely place electrodes at the pial surface, such that fMRI signal from the correct components of each gyrus are assigned to a given electrode. Additionally, distortion in fMRI images due to magnetic susceptibility inhomogeneity must be corrected to achieve correct alignment with structural anatomy and thus the electrodes. Finally, fMRI data processed onto the cortical surface must be projected to individual electrodes by computing the appropriate contribution of each surface element. Solutions to all of these problems are discussed in detail in Chapter 2.

1.4.2 Defining fMRI Resting State Networks in Individual Subjects

The distribution of brain regions covered by electrode grids is unique to each ECoG patient. Further, the spatial distribution of functional connectivity differs by individuals (Mennes et al., 2010, Mueller et al., 2013). Therefore, for the present work it is important to define resting state network topography in individual subjects. Concurrently, it is important to guarantee that the equivalent network component is identified across subjects.

Two analytic strategies, seed-based correlation mapping Biswal (Biswal et al., 2010) and spatial independent components analysis (sICA) (Beckmann, 2012), have so far dominated the field of resting state fMRI. RSNs obtained by sICA are theoretically unbiased by prior assumptions. However, ICA is not robust at the single subject level; results obtained by this technique invariably are reported at the group level. Seed-based correlation mapping uses priors if it is limited to only a few seeds. However, systematically defining many seeds over the entire brain (Wig et al., 2014) and analyzing the results using graph theoretic tools (Power et al., 2011) or inner product based clustering (Yeo et al., 2011, Lee et al., 2012) effectively achieves independence from priors. Both ICA and systematic seed-based correlation mapping exemplify unsupervised learning. Therefore, RSNs obtained by these methods may differ not only in topography (i.e., extent and shape), but also in topology (i.e., number of distinct nodes making up a single RSN), depending on the granularity of the recovered components within the modular hierarchy of RSNs (Meunier et al., 2010). Such inconsistencies stem from the fact that unsupervised learning procedures are not constrained to a particular topological scale; therefore, some *post-hoc* classification strategy (e.g., template matching) must be used to establish RSN identity.

We developed a fundamentally novel method where the objective is not to discover RSNs nor to study their functional relevance, but rather to map the topography of known RSNs in individuals. To this end, we trained a multi-layer perceptron (MLP) to estimate RSN memberships of brain loci on the basis of BOLD correlation maps. After training, the MLP decision boundaries are fixed; thus, subsequent results are guaranteed to represent the same entity (at the same topological scale) across individuals or populations. The development and application of this method are described in Chapter 3. Subsequently, this method is used to define RSN topography in ECoG subjects studied in later chapters.

1.5 Summary

In summary, current knowledge of the electrophysiologic basis of RSNs is incomplete; relatively few RSNs have been invasively explored in humans, and in a limited range of frequencies. We will systematically investigate this fundamental issue by studying associative as well as primary sensorimotor networks in a wide range of frequencies.

1.6 Organization of the Dissertation

In the following chapters, we first establish an approach to precisely coregister intracranial electrodes to fMRI data (Chapter 2). We then created a novel machine learning approach to define resting state networks in individual subjects (Chapter 3). This approach is validated with cortical stimulation in clinical electrocorticography (ECoG) patients (Chapter 4). Spontaneous ECoG data are then analyzed with respect to fMRI time-series and fMRI-defined RSNs in order to illustrate novel ECoG correlates of fMRI for both local field potentials and band-limited power (BLP) envelopes (Chapter 5). In Chapter 6, we show that the spectral specificity of these resting state ECoG correlates link classic brain rhythms with large-scale functional domains. Finally, in Chapter 7 we show that the frequencies and topographies of spontaneous ECoG correlations specifically recapitulate the spectral and spatial structure of task responses within individual subjects.

The range of potential applications of a study of basic brain physiology cannot be predicted with certainty. A possible outcome of this work is the demonstration that the brain makes use of spectral specificity among networks to create communication channels in different functional systems. Future work would ultimately aim to understand how the brain makes use of these 'channels' to separate and integrate information. While we do not expect the results of this investigation to be simple (e.g. each network assigned to a specific frequency), we believe it is of great scientific importance to understand the relative distribution of frequencies of different functional systems; determining these distributions and their relationship to evoked activity is the goal of this project. A deeper understanding of the intricate structure of spontaneous activity and its modulation by tasks is fundamental to advance systems neuroscience.

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Chapter 2: Co-registration of Electrocorticography with Functional Magnetic Resonance Imaging

2.1 Introduction

Until very recently, ECoG studies localized electrodes of interest either based on cortical landmarks from intraoperative photos or skull landmark atlas registration (Canolty, Knight 2008; Ray & Crone, 2009; Brovelli et al, 2005). There have been attempts to better co-register ECoG electrodes with the cortical anatomy using CT localization (Hermes, Ramsey 2010, He et al. 2008). The method we have developed allows for the precise alignment of the subdural grid to the surface of the brain, and is similar in concept to the methods used by Hermes et al. and He et al. However, previous ECoG-fMRI studies sampled fMRI data under electrodes using binary spherical masks placed under each electrode. We have substantially improved this method by accounting for surface geometry of the cortical ribbon in localizing the fMRI signal and by using a surface-to-electrode sampling method informed by cortical dipole geometry. The present methodology has been extensively optimized, where feasible, for automated operation and visualization to minimize operator time while maximizing supervision.

2.2 CT to Structural MRI Registration

Preoperative MP-RAGEs were acquired using standard clinical protocols. CT images were acquired prior to removal of the electrode grid. CTs were transformed to atlas space using a cross-modal procedure based on alignment of image gradients (Rowland, 2005) in which the CT image is aligned to the individual subject MP-RAGE, and the MP-RAGE is then transformed to an atlas-space representative target (Talairach and Tournoux, 1988) using a 12-parameter affine transformation (see Figure 2.1 B/C). The transform matrices were composed so that the registration could be performed in a single step.



Figure 2.1. ECoG coregistration methodology.

A) Intraoperative photo taken at the time of the 8x8 macro-grid implantation. B & C) Coregistration of CT (B) image to MP-RAGE (C). Electrode artifacts can be plainly seen in the CT image (left). The red outline qualitatively indicates the tracing of bone in the CT and MRI scans.
D) Electrode isosurface illustrated by Slicer3D. Artifacts from wires are visible. E) Segmented electrode isosurface illustrated by Slicer3D (radiographic orientation). The electrodes were segmented by a multi-step algorithm to remove wires from the image, and to separate defects connecting neighboring electrodes. The electrode coordinates were extracted by taking the center of mass of each segmented electrode.

2.3 Electrode Segmentation

Electrodes in the CT image were often found in contiguous clusters due to artifact induced by the presence of wires and artifacts from the extreme intensity of metal electrodes in x-ray based modalities. The presence of wires effectively 'bridging' electrodes together into contiguous clusters (evident in Fig. 2.1D) necessitates image post-processing before attempting to cluster the image into electrodes. A highly robust electrode segmention can be achieved by a combination of a Gaussian blur (with a kernel radius matched to the electrode size, or at least substantially larger than the wire thickness), harsh thresholding (generally >3000 in CT intensity), voxel erosion, and voxel dilation. In practice, a Gaussian blur and thresholding (occasionally requiring manual adjustment) adequately separated electrodes in the vast majority of cases. In rare instances strip and grid electodes were overlapping or closer than the precision of CT image voxels; in these cases an automated procedure could not separate the electrodes and knowledge of the implanted electrode configuration was required to inform either a manual editing of the image (to separate nearby electrodes) or direct localization of electrode coordinates by an operator viewing individual slices of the CT image. After post-processing, center-of-mass coordinates from clusters of face-contiguous voxels were isolated using an in-house clustering algorithm.

Coordinates extracted from the thresholded CT image contain numerous artifacts from other metallic objects in the image (e.g., wires and clips). A supervised electrode trimming tool (designed in MATLAB) was used to remove under 3D visualization (Fig.2.2A,B), and facilitate sorting and labeling electrodes. After removing debris (Fig. 2.2C), the grids and strips are assigned constituent electrodes.

Electrode labeling was assisted by an automated sorting algorithm that flattens and rotates the electrode grid by the following procedure:

- 1. Inter-electrode distances are computed between all electrode pairs.
- Distances were thresholded under 10mm*√2 to isolate vectors of neighboring electrode pairs (Fig 2.2D, left).
- The angles of these vectors were clustered to into orthogonal vectors of the grid lattice geometry (Figure 2.2D, middle). These clustered angles were averaged to estimate the first two eigenvectors of the grid geometry (blue and red vectors).
- 4. Electrodes were projected onto these eigenvectors, placing each electrode coordinate in a rotated 2-dimensional space. (Fig 2.2D right).
- Electrodes are sorted independently along the two principal dimension assigned indices (Fig 2.2E) based on the grid orientation defined with the GUI (specified by electrodes 1 and 2, red circles).



Figure 2.2. Electrode selection and sorting.

This interface decreases the time to segment and label electrodes from 1-2 hours of user input (observing raw CT images or plain radiographs) to under 1 minute. **A**) Centers of mass of all contiguous regions passing threshold displayed on a semi-transparent atlas template. **B**) 2D projection of loci from **A**, colored by distance in the X direction for easier removal of non-grid coordinates (various removal methods illustrated in **B**). **C**) Selected electrodes after manual selection of first two electrode indices. **D**) Quality assurance display for sorting algorithm illustrating selected neighbor-neighbor vectors (left), clustering of vectors to find mean orthogonal vectors (middle), and initial indices (right). **E**) Final electrode indices after sorting.

2.4 Deformation Correction

Due to rigidity of the grid materials compared to brain tissue as well as the mechanical forces of fluid accumulation and tension in the dura, the locations of the electrodes at the time of CT acquisition (post-implant) were generally displaced inward relative to the location of the subject's cortical surface at the time of MRI acquistion (pre-operative). To correct for this, electrode coordinates were projected to the surface of the brain as defined in the MR image, such that they were in register with respect to BOLD data acquired pre-operatively. The surface anatomy used in this procedure was extracted using Freesurfer 5 (red surface, Fig 3A); the projection target (grey semitransparent wrapping) was generated by a morphological closing operation performed on the pial surface. Electrodes were projected along a path normal to the local electrode grid curvature (average of nearby tesselated faces of the electrode grid) (Fig. 2.3B) until reaching the electrode target (Fig. 2.3C).



Figure 2.3. Projection of electrodes to cortical surface.

A) Illustration of cortical outer surface (semi-transparent) overlying pial surface (pia colored red for visualization of outer surface). **B)** Projection of electrode coordinates to outer surface using local mean normal of grid tesselation. **C)** Final location of electrode coordinates on pial surface.

2.5 Surface to Electrode Sampling

With the ECoG electrodes correctly registered to the pial surface (Fig 2.4A), a procedure was constructed to relate surface-processed fMRI timeseries (see Chapter 3) as well as cortical topographies in general to electrode data. Surface data were projected to each electrode according to the expected relative contribution of each brain locus (i.e., cortical surface element) modeled under electrostatic assumptions. The cerebral grey matter was modeled as a sheet of diploes oriented normal to the cortical mid-thickness surface. In the present work, the angular component of the dipole contribution was ignored because it was empirically determined that small errors in electrode registration lateral to the cortical sheet could lead to unstable (suppressed) contributions. This is acceptable because loci outside of a relatively smooth surface are necessarily most proximal to surface elements with normal vectors directed toward the locus: the impact of the sign error for negative contributions (which are necessarily far from the electrode) is minimal. Thus, the forward solution for modeling the contribution of surface loci to electrodes was modeled by solely by the inverse square of the distance from cortical midthickness surface vertices (r_i) to points on the electrode surface (r_i) . The contribution to electrode *e* of cortical surface vertices *j* were found by integrating over all elements *i* of the electrode surface S_e :

$$w_{ej} = \int_{i \in S_e} \left\| r_i - r_j \right\|^{-2} dS_e$$

A. Pial Registration B. Mid-thickness weighting

C. Total Coverage



Figure 2.4. Precision Electrode-to-Surface Registration

A. Segmented electrode coordinates after projection to the smoothed pial surface (see Extended Data Fig. 2). **B**. Electrode models (registered to pial surface) overlaid on mid-thickness surface. The surface sampling function for each electrode was defined as the inverse square of the distance from each electrode surface locus (\vec{r}_e) to each mid cortical thickness surface locus (\vec{r}_{mid}). The relative weighting function for an individual electrode (after integrating over the electrode surface, \vec{r}_e) is indicated by the surface hue. Note that the contribution to each electrode is strongly local. **C.** Sum of weight functions across all electrodes in one subject. This computation is not used for analyses, but is presented here to illustrate electrode coverage.

The surface map of weights for electrode $e, w_{e.}$, was normalized to unit sum:

$$\overline{w}_{ej} = \frac{w_{ej}}{\sum_{j \in S} w_{ej}}$$

These weights were expressed as a matrix, W, of dimension [electrodes × cortical vertices]. The relative weights for one electrode, w_{e_1} , are illustrated in Figure 2.4B.

2.5 fMRI Distortion Correction

Echo planar imaging (EPI) sequences used in fMRI BOLD image acquisition produce significant image distortion and dropout due to inhomogeneities of the magnetic susceptibility of nearby tissue types (e.g. air, bone, CSF). In order to better align the fMRI data to the cortical surface geometry computed from structural T1 imaging, distortion correction was performed using non-linear registration methods in the FUGUE module in FSL (Jenkinson et al., 2012). Field maps were approximated using the technique described by Gholipour and colleagues (Gholipour et al., 2008). Distortion correction and motion correction were combined in one resampling step to generate volumetric time-series in Talairach atlas space ($3 \times 3 \times 3 \text{ mm}^3$ cubic voxels).

To determine whether electrodes lie over regions of significant fMRI signal dropout, an EPI isosurface was computed at an intensity threshold approximating the surface of the brain. Electrodes were projected to this surface using the methods described above - electrodes over significant dropout (>5mm to isosurface) were generally excluded from any ECoG-fMRI analyses.

fMRI timeseries were prepared for comparison to ECoG data by ribbon-constrained volume to surface resampling using the Human Connectome Project pipeline (Glasser et al., 2013). W was used to sample cortical surface maps of each frame of the fMRI timeseries, f(t), onto the space of electrodes: $f_e(t) = Wf(t)$.

 $f_e(t)$ was subsequently used to compute the fMRI temporal correlation matrix in electrode space, thereby ensuring that the fMRI and ECoG data were analyzed identically. The weights were also used for sampling RSN network membership estimates (defined in chapter 3) to electrodes for classifying electrodes into RSNs, and for illustrative purposes to create surface displays of correlation maps computed in electrode space (chapters 5 and 6).

2.6 Summary

The methods in this chapter provide a comprehensive approach to registering intracranial electrodes to multiple modalities of neuroimaging data. The entire process of registering

electrodes to fMRI data is summarized in Fig 2.5: the structural T1 segmented using Freesurfer (Fig 2.5.1) is registered with the CT with implanted electrodes (Figure 2.5.2) using a rigid body transform. Electrodes are shown after correction for electrode displacement relative to the T1 via projection to the pial surface. Finally, to correct for EPI distortion due to magnetic susceptibility inhomogeneity, EPI data are unwarped with a field map (Fig 2.5.3). The composite figure (Fig 2.5, top) shows these data types superimposed. For illustrative purposes sections of colored spheres indicate the inverse square weighting of cortical tissue in volume space. Locations of EPI dropout are also evident (red asterisk).

Fig 2.6A illustrates a similar scheme to Fig 2.5 shown in the space of voxels. Figure 2.6 also illustrates potential applications of the electrode sampling functions to fMRI timeseries and RSN topography data. For example, in Figure 2.6B the fMRI timeseries sampled to individual electrodes was correlated with every region in the brain to make a seed-based correlation map. Figure 2.6C shows the results of sampling RSN scores (see Chapter 3) to electrodes as scalar values of RSN membership (coded by color saturation) and resulting winner take all assignments overlaid on RSN topography estimates in individual subjects (Figure 2.6D).


Figure 2.6 Registration of Electrodes to EPI Data.

Blue surface: pial reconstruction. Red markers: electrodes registered to pial surface. White markers: electrodes relative to EPI isosurface for detection of nearby magnetic susceptibility artifact. Green arrows: smoothed pial surface normals. Yellow/orange/red contours: radial EPI sampling functions. Note the correspondence of gyral features in EPI data (orbital region in coronal section cut-away; top panel) with white pial surface outline in a region of EPI dropout (red asterisk).



Figure 2.7. Assignment of RSN membership to electrodes.

A: fMRI timeseries are sampled from voxels onto electrodes, modeling grey matter as a superposition of dipoles normal to the cortical surface. r: position vector for the voxel (v) or electrode (e); n: normal vector at nearest pial surface locus; θ : dipole angle. B: fMRI correlation maps generated using the timeseries sampled in A onto electrodes (white circles) as seeds. C: Each correlation map is analyzed (see text) to give RSN membership scores for each electrode. Opacity indicates relative score scaled [0,1]. The bottom row indicates the RSN with maximum score for determining subjects with valid RSN coverage and for illustration (D). D: Electrode coverage summary for 3 participants. RSN scores are determined for every voxel and sampled to the pial surface for context. Labels (a-d) indicate electrodes with example correlation maps given in B and scores indicated by arrows in C.

Chapter 3: Resting State Network Estimation in Individual Subjects

Carl D. Hacker, Timothy O. Laumann, Nicholas P. Szrama, Antonello Baldassarre, Abraham Z. Snyder, Eric C. Leuthardt, Maurizio Corbetta This project was originally conceived by CDH, TOL, and NPS in the Biological Neural Computation course taught by Barani Raman. CDH, AZS, TOL, ECL, and MC contributed to writing and revision. CDH, TOL, NPS, and AZS performed analyses. AB contributed methods and data for RSN definition.

Abstract

Resting-state functional magnetic resonance imaging (fMRI) has been used to study brain networks associated with both normal and pathological cognitive function. The objective of this work is to reliably compute resting state network (RSN) topography in single participants. We trained a supervised classifier (multi-layer perceptron; MLP) to associate blood oxygen level dependent (BOLD) correlation maps corresponding to pre-defined seeds with specific RSN identities. Hard classification of maps obtained from *a priori* seeds was highly reliable across new participants. Interestingly, continuous estimates of RSN membership retained substantial residual error. This result is consistent with the view that RSNs are hierarchically organized, and therefore not fully separable into spatially independent components. After training on *a priori* seed-based maps, we propagated voxel-wise correlation maps through the MLP to produce estimates of RSN membership throughout the brain. The MLP generated RSN topography estimates in individuals consistent with previous studies, even in brain regions not represented in the training data. This method could be used in future studies to relate RSN topography to other measures of functional brain organization (e.g., task-evoked responses, stimulation mapping, and deficits associated with lesions) in individuals. The multi-layer perceptron was directly compared to two alternative voxel classification procedures, specifically, dual regression and linear discriminant analysis; the perceptron generated more spatially specific RSN maps than either alternative.

3.1 Introduction

Biswal and colleagues first described resting state functional magnetic resonance imaging (fMRI) in 1995 (Biswal et al., 1995). The literature in this field has since been growing exponentially (Snyder and Raichle, 2012). Most of this work has been directed towards describing the statistical properties of intrinsic blood oxygenation level dependent (BOLD) signal fluctuations in health and disease (Biswal et al., 2010; Fox and Greicius, 2010; Pievani et al., 2011; Zhang and Raichle, 2010). Spontaneous BOLD activity recapitulates, in the topographies of its temporal covariance structure, task-based fMRI responses to a wide variety of behavioral paradigms (Smith et al., 2009). These topographies currently are known as resting state networks (RSNs) or, equivalently, intrinsic connectivity networks (ICNs). RSNs have now been mapped over virtually all of the cerebral cortex as well as many subcortical structures including the cerebellum (Buckner et al., 2011; Choi et al., 2012; Lee et al., 2012; Power et al., 2011; Yeo et al., 2011). Critically, although RSN topographies differ across individuals (Mennes et al., 2010; Mueller et al., 2013), previously reported results generally have been reported at the group level. Effectively capturing individual differences in RSN organization would enhance the study of how intrinsic activity accounts for individual differences in human behavior and cognition.

Reliable RSN mapping in individuals has multiple applications, for example, in the study of the physiological basis of inter-individual differences in cognition, e.g., (Cole et al., 2012; Koyama

et al., 2011). Similarly, improved RSN mapping in individuals could be useful in the study of how focal lesions, e.g., strokes, lead to performance deficits (Carter et al., 2010; Golestani et al., 2013; He et al., 2007); such studies are difficult at the group level because of lesion heterogeneity. Yet another application is to improve the delineation of "eloquent" cortex prior to neurosurgery, to potentially reduce iatrogenic deficits (Otten et al., 2012; Tie et al., 2013; Zhang et al., 2009). Pre-operative task-fMRI has been used for this purpose (Wurnig et al., 2013) but often fails because patients are unable to comply with task paradigms. Lastly, individual RSN mapping could enhance functional co-registration, i.e., using RSN features to refine anatomical registration (Conroy et al., 2013; Sabuncu et al., 2010).

Two analytic strategies, seed-based correlation mapping (Biswal et al., 2010) and spatial independent components analysis (sICA) (Beckmann, 2012), have so far dominated the field of resting state fMRI. RSNs obtained by sICA are theoretically unbiased by prior assumptions. However, ICA is not robust at the single subject level; results obtained by this technique invariably are reported at the group level. Seed-based correlation mapping uses priors if it is limited to only a few seeds. However, systematically defining many seeds over the entire brain (Wig et al., 2013) and analyzing the results using graph theoretic tools (Power et al., 2011) or inner product based clustering (Lee et al., 2012; Yeo et al., 2011) effectively achieves independence from priors. Both ICA and systematic seed-based correlation mapping exemplify unsupervised learning. Therefore, RSNs obtained by these methods may differ not only in topography (i.e., extent and shape), but also in topology (i.e., number of distinct nodes making up a single RSN), depending on the granularity of the recovered components within the modular hierarchy of RSNs (Meunier et al., 2010). To illustrate, the default mode network (DMN) is a

constellation of regions including the posterior cingulate-precuneus cortex (PCC), midline prefrontal cortex, lateral parietal cortex, superior frontal cortex and posterior cerebellum. The DMN may be recovered in its entirety (Fox et al., 2005) using highly supervised methods. However, unsupervised strategies variably recover the DMN in fragments (Kahn et al., 2008; Smith et al., 2009), or combined with fragments of other networks (Doucet et al., 2011; Lee et al., 2012; Yeo et al., 2011). Such inconsistencies stem from the fact that unsupervised learning procedures are not constrained to a particular topological scale; therefore, some *post-hoc* classification strategy (e.g., template matching) must be used to establish RSN identity.

The present work is fundamentally different in that the objective is not to discover RSNs nor to study their functional relevance, but rather to map the topography of known RSNs in individuals. To this end, we trained a multi-layer perceptron (MLP) to estimate RSN memberships of brain loci on the basis of BOLD correlation maps. A perceptron is a feedforward artificial neural network, originally modeled on the human visual system, trained to associate weighted sums of input features with pre-defined output classes (Rosenblatt, 1958). After training, the MLP decision boundaries are fixed; thus, subsequent results are guaranteed to represent the same entity (at the same topological scale) across individuals or populations. Perhaps the best-known application of perceptrons is to recognize (classify) handwritten digits (Lecun et al., 1989). This application has obvious utility in automatic routing of letters at the post office. To distinguish between supervised vs. unsupervised learning, consider discovering the characters used to represent numbers in the decimal system by analysis of a large sample of addressed letters. This is very different from training a perceptron to read (classify) known numerals, e.g., zip codes on addressed letters. Analogously, RSN discovery, using group sICA or any other unsupervised method, is very different from preparing a trained MLP to map known RSNs in new subjects.

In the above example, each character must represent one and only one numeral. However, we do not assume that every brain region belongs to a single RSN. We allow each locus in the brain to belong to any RSN to a variable degree. Accordingly, RSN membership estimation represents regression rather than classification. However, classification and regression are closely related mathematically. MLP outputs, which approximate posterior probabilities of class membership (Ruck et al., 1990), can be converted to hard classifications by identifying the output class of greatest magnitude. We report both continuous RSN estimates and hard classifications ("winner-take-all" maps). MLP performance was characterized by residual error for the former and receiver operating characteristic (ROC) analysis for the latter (Section 3.2.4).

Our methodology represents a solution to an engineering problem, namely, mapping RSNs in individuals. However, MLP training performance offers valuable information about the structure and separability of resting-state networks. Differential performance across RSNs may provide insight into their relative inter-subject variability and complexity. MLP performance also provides an objective measure of data quality that can be used to study the effects of varying acquisition and preprocessing methodologies. We demonstrate this concept by determining the quantity of BOLD data required to reliably compute RSN topography in individual subjects. Similarly, we empirically determine the optimal ROI size for generation of correlation map training data. As a final result, two alternative strategies for extending group-level RSN topographies to individuals (linear discriminant analysis and dual regression) are compared to the MLP. This comparison shows that the MLP provides superior RSN mapping specificity.

3.2 Methods

The Methods section is organized as follows: We first describe the fMRI datasets (section 2.1) and neuroimaging methods (2.2). We next describe the task-fMRI meta-analyses (2.3) used to isolate seed ROIs. These seeds were used to generate the MLP training data. MLP-specific methodology is divided into design (2.4) and application (2.5). The design phase (2.4) used correlation maps corresponding to seed ROIs with categorical RSN labels to train, evaluate, and optimize the MLP (Section 3.2.4). Application of the trained perceptron to individuals generated voxel-wise estimates of RSN membership throughout the brain (3.2.5). MLP results then were compared to dual regression (DR) and linear discriminant analysis (LDA) (3.2.6).

3.2.1 Participants

Perceptron training, optimization and validation used data sets previously acquired at the Neuroimaging Laboratories (NIL) at the Washington University School of Medicine. A second, large validation data set was obtained from the Harvard-MGH Brain Genomics Superstruct Project (Yeo et al., 2011). All patients were young adults screened to exclude neurological impairment and psychotropic medications. Demographic information and acquisition parameters are given in Table 3.1.

Dataset	Training	Optimization	Validation 1	Validation 2 [§]	
Number of Subjects	21 (7M + 14	17 (8M + 9F)	10(4M + 6F)	692 (305M + 387F)	
	F)				
Age in years	27.6 (23-35)	23.1 (18-27)	23.3 ± 3 (SD)	21.4 ± 2.4 (SD)	
Scanner	Allegra	Allegra	Allegra	Tim Trio	
Acquisition voxel	$(4 \text{ mm})^3$	$(4 \text{ mm})^3$	$(4 \text{ mm})^3$	$(3 \text{ mm})^3$	
size					
Flip angle	90°	90°	90°	85°	
Repetition Time (sec)	2.16	2.16	3.03*	3.00	
Number of frames	128×6 runs	194×4 runs	110×9 runs	124×2 runs	
Citation (Lee et al.,		(Fox and Raichle,	(Fox et al., 2005)	(Yeo et al., 2011)	
	2012)	2007)			

Table 3.1. Characteristics of the Training, Test and Validation datasets.

*Validation data set 1 included a one second pause between frames to accommodate simultaneous electroencephalography (EEG) recording. [§] Validation data set 2 was acquired at Harvard-MGH by the Brain Genomics Superstruct Project.

3.2.2 Neuroimaging methods

MRI acquisition

Imaging was performed with a 3T Allegra (NIL) or Tim Trio (Harvard-MGH) scanner.

Functional images were acquired using a BOLD contrast sensitive gradient echo echo-planar sequence [parameters listed in Table 3.1] during which participants were instructed to fixate on a visual cross-hair, remain still and not fall asleep. Anatomical imaging included one sagittal T1-weighted magnetization prepared rapid gradient echo (MP–RAGE) scan (T1W) and one T2-weighted scan (T2W).

fMRI preprocessing

Initial fMRI preprocessing followed conventional practice (Shulman et al., 2010).

Briefly, this included compensation for slice-dependent time shifts, elimination of systematic odd-even slice intensity differences due to interleaved acquisition (Supplemental text section

S2.2.2) and rigid body correction of head movement within and across runs. Atlas transformation was achieved by composition of affine transforms connecting the fMRI volumes with the T2W and T1W structural images. Head movement correction was included with the atlas transformation in a single resampling that generated volumetric timeseries in (3mm)³ atlas space. Additional preprocessing in preparation for correlation mapping included spatial smoothing (6 mm full width at half maximum (FWHM) Gaussian blur in each direction), voxel-wise removal of linear trends over each fMRI run and temporal low-pass filtering retaining frequencies below 0.1 Hz.

Spurious variance was reduced by regression of nuisance waveforms derived from head motion correction and timeseries extracted from regions (of "non-interest") in white matter and CSF. Nuisance regressors included also the BOLD timeseries averaged over the brain (Fox et al., 2005), i.e., global signal regression (GSR). Thus, all computed correlations were effectively order 1 partial correlations controlling for variance shared across the brain. GSR has been criticized on the grounds that it artificially generates anticorrelations (Murphy et al., 2009). However, GSR fits well as a step preceding principal component analysis because it generates approximately zero-centered correlation distributions. As well, GSR enhances the spatial specificity in subcortical seed regions and reduces structured noise (Fox et al., 2009). The question of whether the left tail of a zero-centered correlation distribution ("anticorrelations") is "false" (Damoiseaux and Greicius, 2009) or "tenuously interpretable" (Yeo et al., 2011) is irrelevant in the context of supervised learning.

Correlation maps were computed using standard seed-based procedures (Fox et al., 2009), i.e., by correlating the timeseries averaged over all voxels within the seed against all other

voxels, excluding the first 5 (pre-magnetization steady-state) frames of each fMRI run. Seeds were 5 mm radius spheres initially and 10.5 mm radius spheres after optimization (see section 3.5.4). Additionally, we employed frame-censoring with a threshold of 0.5% root mean square frame-to-frame intensity change (Power et al., 2012; Smyser et al., 2010). Frame-censoring excluded $3.8 \pm 1.1\%$ of all magnetization steady-state frames from the correlation mapping computations. Correlation maps were Fisher z-transformed prior to further analyses.

Surface processing and gray matter definition

Cortical reconstruction and volume segmentation were performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999). Adequate segmentation was verified by inspection of the FreeSurfer-generated results in all datasets (Table 3.1). Cortical and subcortical gray matter regions were selected from the Training set segmentations, thresholded to obtain a conjunction of 30% of subjects, and then masked with an image of the average BOLD signal intensity across all subjects, thresholded at 80% of the mode value. This last step removed from consideration brain areas in which the BOLD signal is unreliable because of susceptibility artifacts. The resulting 30,981 voxels constituted the grey matter mask. For purposes of visualization, individual surfaces were deformed to a common space (Van Essen et al., 2012), producing consistent assignment of surface vertex indices with respect to gyral features across subjects. Final volumetric results for each subject were sampled onto surface vertices by cubic spline interpolation onto mid-thickness cortical surface coordinates.

3.2.3 Meta-analysis of task fMRI and generation of training data

ROIs representing distinct RSNs were isolated by meta-analysis of task-fMRI responses. We initially targeted 10 functional systems, each represented by a variable number of response foci derived from the literature (Table 3.2). The initial set of response foci was refined to ensure that all ROIs assigned to the same RSN generated maximally similar correlation maps and that ROIs assigned to different RSNs generated distinct correlation maps. These criteria yielded 169 ROIs representing 7 RSNs with high intra- and low inter-network correlation (Figures 3.1 and 3.2; see Supplemental text section for algorithmic details). Thus, 3 of the original 10 networks were subsumed into the remaining networks. To these were added a nuisance category consisting of 6 ROIs in cerebrospinal fluid (CSF) spaces. The latter enabled the MLP to separate correlation patterns representing CSF vs. true RSNs. Computing correlation maps for each of the 175 seed regions in all 21 Training subjects produced 3,675 images used as training data. Each image in the Training set was masked to include only grey matter voxels, producing a $3,675 \times 30,981$ matrix. Similarly, 175 regions \cdot 17 subjects = 2,975 images, 175 regions \cdot 10 subjects = 1,750 images and 175 regions \cdot 692 subjects = 121,100 images, were computed in the Optimization, Validation 1, and Validation 2 data sets, respectively.

RSN	Expanded acronym	Citation	Task paradigm	Task contrast	Final seed ROIs
DAN	Dorsal Attention Network	(Shulman et al., 2009; Tosoni et al., 2012)	Rapid Serial Visual Presentation (RSVP)	Cue Type x Time	
		(Shulman et al., 2009; Tosoni et al., 2012)	Rapid Serial Visual Presentation (RSVP)	Cue Location x Cue Type x Time	28
		(Astafiev et al., 2004; Corbetta et al., 2000; Kincade et al., 2005)	Posner Cueing Task	Time	
VAN	Ventral Attention Network	(Astafiev et al., 2004; Corbetta et al., 2000; Kincade et al., 2005)	Posner Cueing Task	Invalid vs. Valid	15
		(Dosenbach et al., 2007)	10 different cognitive control tasks*	Graph theoretic analysis	
SMN	Sensori- Motor	(Corbetta et al., 2000; Kincade et al., 2005)	Posner Cueing Task	Motor response	20
	Network	(Petacchi et al., 2005)	Various auditory stimuli	Stimulation vs. Control	- 39
VIS	Visual network	(Sylvester et al., 2008; Sylvester et al., 2007, 2009)	Visual Localizer	Discrete visual stimuli	30
FPC	Fronto- Parietal Control network	(Dosenbach et al., 2007)	10 different cognitive control tasks*	Graph theoretic analysis	12
LAN	Language network	(Sestieri et al., 2011; Sestieri et al., 2010)	Perceptual vs. Episodic Memory Search Paradigm	Sentence reading	13
DM N	Default Mode Network	(Sestieri et al., 2011; Sestieri et al., 2010)	Perceptual vs. Episodic Memory Search Paradigm	Memory retrieval	32

Table 3.2. Studies of functional co-activation used to generate seed ROIs.*Regions reported by Dosenbach and colleagues (2007) were themselves the result of a metaanalysis.



Figure 3.1. Seed ROIs for Generation of Correlation Map Data. Seed ROIs resulting from a meta-analysis of task foci (see section 2.3) were defined in volume space. To visualize the surface variability of volume-defined regions, 5 mm radius spherical ROIs centered on stereotactically defined coordinates were projected onto surface reconstructions for each individual. Transparent regions indicate at least 20% surface overlap of ROIs across subjects. Opaque regions indicate at least 50% overlap. Figure S1 shows both hemispheres in slice format.

3.2.4 MLP design

The core of a perceptron is an artificial neural network consisting of an input, hidden, and output layer, each consisting of nodes fully connecting to the next layer (all-to-all feed-forward). Training samples are passed into this feed-forward network and the output is compared to the *a priori* assigned RSN label. The error in this comparison is used to update the connection weights, between layers to increase the performance of the MLP (Rumelhart et al., 1986).

3.2.4.1 Principal components analysis (PCA) preprocessing

Expressing MLP inputs as eigenvector weights, in other words, preceding the MLP proper with a PCA layer, enabled dimensionality reduction without significant loss of information (Erkmen and Yıldırım, 2008). PCA preprocessing allowed the use of fewer hidden layer nodes, reduced the size of the weight matrices and accelerated the training process by a factor of ~500. PCA was performed on the matrix of gray matter masked correlation images

constituting the Training set (21 subjects \cdot 175 seeds = 3,675 images, each image comprised of 30,981 gray matter voxels). Each correlation map then was represented as its projection along some number of PCs. The number of PCs, and correspondingly, the number of input nodes (N_i) was a hyper-parameter subject to optimization (see section 3.2.4). The number of PCs used to optimize global performance (minimize squared error summed over classes) was 2,500 (see Section 3.2.4).

3.2.4.2 MLP training

Training data, represented as vectors in PCA space, were presented to the MLP input layer. Each training example was associated with a desired output value determined by its *a priori* assigned RSN label. The MLP generated 8 (7 RSN and one CSF) output values for each training example. During training, these outputs were compared to the desired values (1 at the node corresponding to the *a priori* assigned label, 0 at other nodes). This comparison generated error signals used to update the connection weights. Algorithmic details are given in Appendix A, which includes a detailed schematic of the present MLP structure (Figure 3.A.1).

3.2.4.3 Quantitation of MLP performance

MLP error was defined as the difference between the MLP outputs and *a priori* assigned RSN labels (see above). Total RSN estimation performance was evaluated as root mean square (RMS) error aggregated over all output classes, across all training samples (participants × ROIs). Similar performance measures were computed for individual RSNs and individually for each participant. Classification performance (in the winner-take-all sense) was quantified using receiver operator characteristic (ROC) analysis. ROC curves define the relation between the true positive fraction (TPF) vs. the false positive fraction (FPF) across a range of thresholds. An ROC curve was generated for each RSN. Thus, e.g., for the DAN, the TPF was the fraction of DAN training inputs above threshold at the DAN output node. Similarly, the FPF was the fraction of non-DAN inputs above threshold at the DAN output node. Thus, the area under the ROC curve (AUC) was used as a summary statistic representing classification performance for each RSN.

Training was paused at logarithmically spaced intervals during the training process and RMS error as well as AUC were calculated in the Optimization data set. This procedure produced training trajectories indicating the performance over-all and for each RSN throughout the training process.

Architecture selection

The number of PCs sampled (N_i) , and the number of nodes in the hidden layer (N_h) constitute hyper-parameters subject to optimization. Overall RMS error was evaluated over a densely sampled $N_i \in [5,6600] \times N_h \in [4,5000]$ space. For each (N_i, N_h) coordinate, a MLP was trained until Optimization set error reached a minimum. This procedure was repeated (minimum of eight repetitions) for each (N_i, N_h) coordinate to identify the architecture with the least error. This procedure identified 2,500 PCs and 22 hidden layer nodes as the optimal architecture (see Supplemental section 3.S2.4.4 and Figure 3.S2). Similar systematic evaluation MLP performance as a function of ROI size identified 10.5mm as the optimum (Figure 10B). Performance optimization by simulated annealing

After identifying the optimal architecture with least error in the Optimization data set, performance was iteratively optimized by simulated annealing (Kirkpatrick et al., 1983), countering the tendency of perceptrons to become trapped in local minima. Mimicking the random movement of atoms aligning in cooling metal, simulated annealing uses random perturbations of model parameters to find the global extremum in an objective function (Geman and Geman, 1984). Perturbations of steadily decreasing size (specified by a 'cooling profile') are guaranteed to find a global minimum, although, in practice, the necessary cooling profile is prohibitively slow (Kirkpatrick, 1984). The cooling profile was designed to ensure that the sum of squares of the connection weights was unaltered by the simulated annealing perturbations and that most weights decreased while a few weights sporadically increased. Additional simulated annealing details are provided in Supplementary content (3.S2.4.5).

Error in the Optimization data was used as heuristic in the above-described iterative optimization procedure. Therefore, to avoid underestimating generalization error, final performance was estimated using a fully independent Validation datasets.

3.2.5 Application of method to individuals

To map RSNs in individual subjects, a correlation map was generated for every voxel in the brain and then propagated through the optimized perceptron. An overall schematic of this process is depicted in Figure 3.2.



Figure 3.2. Single-subject, Voxel-wise Estimation of RSNs Using the Trained MLP. A. Each locus produces one correlation map that ultimately results in N=7 MLP estimates of network membership at that locus. B. Each correlation map is masked to include only grey matter voxels and projected into principal component space. C and D. The masked image is passed through the neural network. See Appendix A and Figure A1 for details of MLP connections and training process. E. Output values converted to percentiles (uniform distribution over 0 to 1 interval) for surface displays. The 8th (nuisance component) MLP output is not illustrated.

3.2.5.1 Whole-brain analysis

Each of the 65,549 voxels in the brain generated a correlation map (Fig. 3.2A). Projecting correlation map values within the gray matter mask (30,981 voxels) into PCA space (see section 2.4.1) yielded 2,500 principal component coefficients (Fig. 3.2B). Thus, for each participant, the data presented to the MLP were contained in a $65,549 \times 2,500$ matrix (same 2,500 dimensional PCA space as used for MLP training). Each individual's data then were propagated through the perceptron (see section 3.2.4). The first layer (Fig. 3.2C) reduced the data to 22 features (65,549 × 22 matrix); the second layer (Fig. 3.2D) produced MLP outputs (65,549 × 8 matrix). These outputs were used to compute RMS error. RMS error served as the feedback signal during training and was also used to assess MLP performance. For display purposes, MLP output values

were rank-order transformed to a uniform [0,1] distribution within each network. This transformation emphasizes topography rather than magnitude.

3.2.5.2 Group-level analyses

To visualize group-level results, RSN membership estimates were sampled onto the cortical mid-thickness surface for each participant. Averages were then computed across surface vertices. The standard deviation of MLP output values was also calculated vertex-wise to illustrate regions of high variability. To visualize group-level results in sub-cortical structures, MLP output values were averaged voxel-wise across participants. Group-average images were then re-sampled to 1mm cubic voxels and overlaid on a co-registered MNI152 atlas template.

3.2.6 Comparison of the MLP to linear discriminant analysis and dual regression

Linear discriminant analysis (LDA) is a classification algorithm that operates by projecting data onto vectors that maximize the ratio of between-class scatter to within-class scatter (Appendix B). PCA preprocessing is essential in LDA because the dimensionality of the input space (originally, tens of thousands of voxels) must be substantially less than the number of training examples (Belhumeur et al., 1997). By systematic exploration of the feasible PCA dimensionality range, it was determined that the lowest classification error in the Optimization set was obtained with 20 principal components. All present LDA results were obtained with this LDA design.

Dual regression (DR) is a technique commonly used subsequent to group ICA to extend spatial ICs discovered at the group level to individuals. Group ICA is a technique for discovering RSNs whereas the present work is about mapping known RSNs, not about RSN discovery (see Introduction). In fact, the present LAN (see section 3.2.3) typically is not obtained by group ICA, e.g., (Damoiseaux et al., 2006). Nevertheless, DR is algebraically well defined regardless of the origin of the group-level RSNs (Appendix B). Here, we used RSNs derived by meta-analysis of task-fMRI. Seed-based correlation maps were averaged across all participants and across all seed regions representing each class, generating 7 spatial RSN components and one nuisance component. Dual regression was then performed as described in Appendix B (cf. (Zuo et al., 2010)).

Voxel-wise RSN estimates were generated using each technique (MLP, DR, LDA) and converted to a percentile scale as described in section 3.2.5 for visualization. To quantitatively compare performance across methods, RSN estimates were computed for maps generated using the *a priori* ROIs. Seed-based covariance maps were used to evaluate DR performance (Eq. (B.5) in Appendix 3.B); seed-based correlation maps were used to evaluate LDA and MLP performance (Eqs. (B.6) and (B.7)). These evaluations yielded RSN estimates for each seed for each participant for each method. From these values and the associated *a priori* RSN labels, ROC curves and AUC scores were computed for each network (see section 3.2.4).

3.3 Results

3.3.1 MLP training



Figure 3.3. Projection of RSNs into PCA space.

A. Temporal correlation matrix: For each subject, the processed BOLD time-courses were averaged over each seed region. The resulting matrices were averaged across subjects. B. Spatial correlation matrix: For each subject, correlation maps were produced for every seed region. Matrices of spatial correlation between each seed's map were computed, and then averaged across subjects. C. Principal component analysis: PCA was performed on correlation maps, yielding the eigenvectors of the map-to-map spatial covariance matrix. Correlation maps for each seed in each subject were projected onto the PCA components, thus generating a locus in PCA space for each of the 3,675 training images. Color indicates the task analysis from which the region was derived.

3.3.1.1 Statistical properties of the training data

Temporal (Fig 3.3A) and spatial (Fig. 3.3B) correlation maps across seeds revealed distinct clustering corresponding to RSNs. Fig 3B exhibits two major clusters, one corresponding to the DAN, VAN, VIS and SMN networks, and the other corresponding to the FPC, LAN, and DMN networks. This dichotomy corresponds to the first principal component in Fig 3C. In the PC1 \times PC2 plane (Fig. 3C), DAN (purple) and DMN (red) showed little overlap and appeared at opposite ends of the PC1 axis. VAN (magenta) and VIS (green) clusters were highly overlapping in this plane, but well separated in the PC3 \times PC4 plane.



Figure 3.4. MLP Training Trajectories as Reflected in the Optimization Dataset. A. Total RMS error as a function of iteration number. Error decreased monotonically for all networks until reaching a global minimum. The black line represents the total RMS error across all networks. The optimal early stopping point was defined as the global minimum of the total RMS error. B. Change in RMS error for each RSN (sign inverted derivatives with respect to iteration). The plotted values have been normalized by change in mean RMS error (black curve in A). Note sequential appearance of $-\Delta$ RMS error peaks and expanded iteration scale. C: ROC curves plotted in parallel with panel A. AUC values in the Training set asymptotically approached unity (not shown), whereas the Optimization data exhibited local maxima (inset). The black line represents the mean AUC across the 7 RSNs. Iterations index is shown on a logarithmic scale in all plots to emphasize early performance.

3.3.1.2 Training Process

Figure 4 shows the training performance for the perceptron optimized for overall performance (2,500 input PCs, 22 hidden layer nodes). For every correlation map, each perceptron output node value represents an estimate of membership in a particular RSN. Perceptron outputs are initially centered at 0.5; as training progresses, within-class output values increase towards unity, while out-of-class output values decrease towards zero (see Fig. 3.A3). RMS error across RSNs (Fig. 4A, black line) began near 0.5 and decreased monotonically until reaching peak performance (Fig. 4A, black arrow); training beyond this point resulted in overfitting, i.e., decreasing performance (increasing RMS error) in the Optimization dataset despite increasing Training performance (see example in Figure 3.A3).

For all networks, the AUC exhibited transient decrement in performance early in training (Fig. 3.4C). This feature corresponded to transient changes of slope in RMS error but did not

produce concavity (local minima) in Fig. 3.4A. RMS error slopes indicated that class separation was achieved at varying numbers of iterations for different RSNs (Fig. 3.4B). The default mode network (red trace) achieved asymptotic performance earliest, and the language network (orange) latest. Asymptotic performance for the CSF class occurred much later than any true RSN.

3.3.2 MLP performance in the Validation datasets

3.3.2.1 Results in individuals

After completion of training, voxel-wise correlation maps were propagated through the MLP in the Validation datasets. Well-defined RSN topographies were obtained in all Validation dataset 1 participants (exemplars shown in Fig. 3.5). RSN topography summaries are displayed as winner-take-all maps (Fig. 3.5, lower panel). The worst Validation 1 AUC was 0.993 with an RMS error of 17.5%. In Validation dataset 2, the mean AUC was .977 with a SD of 0.0085; RMS error (mean \pm SD) was 19.4% \pm 1.73%. The systematically greater RMS error in Validation dataset 2 is accounted for by systematically less data (12 vs. 48 minutes; see Fig. 10A).







Figure 3.6. MLP SMN Results Obtained in Validation Dataset 2 Individuals. A: Five individuals were selected to represent the correspondence between SMN variability and anatomical variability in the central sulcus (see text for details). MLP SMN scores are displayed overlayed on individual MP-RAGE slices. The bright contour corresponds to the 90th percentile of voxel values. Note: high SMN scores track the shape of the central sulcus (red arrows). B: Correlation between the Talairach Y-coordinate of the central sulcus fundus traced over the path indicated in the right inset figure. The SMN centroid was evaluated over the X-Y range indicated by the left inset figure.

	Training (N=21)		Optimization (N=17)		Validation 1 (N=10)		Validation 2 (N=692)	
Network	Accuracy	Error	Accuracy	Error	Accuracy	Error	Accuracy	Error
	(AUC)	(RMS)	(AUC)	(RMS)	(AUC)	(RMS)	(AUC)	(RMS)
DAN	0.992	15.7%	0.973	20.8%	0.973	21.1%	0.966	23.1%
VAN	0.991	14.9%	0.971	19.6%	0.979	17.7%	0.962	21.0%
SMN	0.998	15.3%	0.988	20.0%	0.994	17.5%	0.983	23.4%
VIS	0.998	11.1%	0.993	14.9%	0.998	12.5%	0.993	16.5%
FPC	0.988	12.7%	0.972	17.1%	0.989	14.8%	0.971	17.7%
LAN	0.993	13.5%	0.985	16.0%	0.991	14.5%	0.979	17.7%
DMN	0.997	13.9%	0.993	19.7%	0.991	17.5%	0.986	20.3%
Mean	0.994	13.6%	0.982	17.8%	0.988	16.2%	0.977	19.5%

Table 3.3. RSN classification (AUC) and estimation (RMS) performance. These values reflect MLP training with 10.5 mm radius seeds (see Figure 10) and optimization with simulated annealing.

Figure 3.6 demonstrates the degree to which the MLP to captures individual variability.

We first compared SMN topography to gyral morphology in 5 participants from Validation

dataset 2. Participants were selected for display in Fig 6A as follows: The distribution of

anterior-posterior (AP) positions the SMN (centroid over Talairach Z coordinate [+30,+45], left

hemisphere, X coordinate < 15) was computed over all participants. One exemplar was randomly selected from each quintile. High SMN values conformed to the detailed morphological features of of the central sulcus in individuals (red arrows, Fig. 3.6A, Z = +53). High SMN values also tracked the AP position of the central sulcus (Fig. 3.6A, Z = +38). To obtain a quantitative measure of this tracking, the Y-coordinate of the SMN centroid and the fundus of the central sulcus were evaluated in Validation dataset 2 participants. The correlation between these positional measures was highly significant (r = 0.70, p < 10⁻¹⁵; Fig. 3.6B). This analysis was performed in [the first anonymized] 100 individuals because it required FreeSurfer segmentation of the cortical surface, which is computationally expensive.





Top: Surface-based average over 100 participants from Validation dataset 2. Middle: Standard deviation of RSN values across subjects. Bottom: Winner-take-all maps depict surfaces with patches colored according to the network with the largest value.



692 participants from Validation dataset 2, displayed in slices. WTA indicates the winner-takeall result (thresholded at 0.7 for the winning value). All seven networks were represented in the cerebellum despite absence of cerebellar seeds in the training data. Note left lateralized cerebral foci and right lateralized cerebellar foci for the language network (white arrows, LAN column); similarly, note right cerebral and left cerebellar foci for the ventral attention network (white arrows, VAN column).

3.3.2.2 Validation results at the group level

Figure 7 shows surface projections of RSN topography estimates averaged over 100 participants in Validation dataset 2. This figure addresses both the central tendency (top row) of each RSN, as well as inter-subject variability (middle row). As expected, average network topographies exhibited higher values (red) near locations of ROIs used to generate training maps (Fig. 3.1). More importantly, high RSN scores (in the top 25%) were consistently found in contiguous regions not used to generate training data. For example, a lateral temporal region was

estimated as fronto-parietal control (Fig. 3.7, top row, FPC column), and high language network estimates were assigned to a dorsal pre-motor region (LAN column). These features are also present in the results in individuals (Fig. 3.5A). The significance of these observations with respect to external validity is discussed below (section 3.4.2).

Further evidence of external validity is shown in Figure 3.8, which includes all 692 participants in Validation dataset 2. For example, high SMN scores were obtained in thalamic voxels approximately corresponding to nucleus ventralis posterior and high VIS scores were obtained in posterior pulvinar (arrows), substantially in agreement with (Zhang et al., 2008). High VAN scores were obtained the dorso-medial nucleus, refining the parcellation in (Zhang et al., 2008), who identified this nucleus as functionally connected with "prefrontal" cortex. The posterior cerebellum (Crus I and II) and the cerebellar tonsils were assigned high DMN scores (Figure 7, Z = -30, Z = -47), in agreement with (Buckner et al., 2011). These results are noteworthy because neither cerebellar nor thalamic ROIs were used to generate training data. Further, no cerebellar voxels were within the grey matter mask, which means that the MLP correctly classified cerebellar voxels purely on the basis of cortical connectivity. High VAN and LAN RSN scores were asymmetrically obtained in the cerebellum (arrows, Z = -30), appropriately contralateral to asymmetric cerebral results (Z = +47).

3.3.3 Comparison of the MLP to alternative RSN estimation schemes

Dual regression (DR) and linear discriminant analysis (LDA) produced RSN topographies that were broadly similar to MLP results at the group level (Fig. 3.9A). However, DR and LDA topographies generally had greater spatial extent and more overlap across networks than the MLP-derived topographies. For example, the DAN network exhibited strong (greater than 90th percentile) values in dorsal SMN regions for both DR and LDA, but not for the MLP method. Similarly, VIS topography extended to SMN and DAN regions in DR results, less so in LDA results, and minimally in MLP results.

A cross-methodological comparison of classification performance in terms of AUC is given in Table 3.4. RSN scores were computed as described in section 3.2.6. These RSN scores were converted to hard classifications by identifying the group-derived map yielding the greatest score for each seed ROI. Linear Projection (LP), the simplest possible method, is included in Table 3.4 for comparison with the other methods (see Linear Projection in Appendix 3.B). LP performance was evaluated using seed-based covariance maps (Eq. (B.1) in Appendix B). This is essentially nearest neighbor classification. That is, LP AUC is approximately equivalent to the probability that a map in, e.g., in PCA space is closest to the group average RSN template (represented by cluster centers in Figure 3.3C).





A. Selected group-average RSN topography estimates computed with dual regression (DR), linear discriminant analysis (LDA), and a multi-layer perceptron (MLP). B. RSN estimates evaluated over *a priori* seed ROIs. Topography estimates for each network (A) were averaged over voxels within each seed. The resulting scores were averaged over subjects and plotted for pairs of RSNs (e.g., SMN vs. VIS scores). Markers are colored based on the prior assignment of each seed. Line segments extend from the voxel-wise median score (50th percentile) to the center of mass of the ROI scores for the two RSNs defining the exhibited plane. Note that only the MLP successfully separates LAN seeds from DMN along the LAN axis. C. Inter-class correlation of RSN scores computed as the Pearson correlation coefficient between pairs of

RSNs. Note that RSN scores are least correlated for the MLP, indicating more complete orthogonalization.

	LP	DR	LDA		MLP	
Network	AUC	AUC	AUC	RMSE	AUC	RMSE
DAN	0.900	0.938	0.953	24.5%	0.973	20.2%
VAN	0.853	0.918	0.958	19.9%	0.971	17.9%
SMN	0.949	0.957	0.989	18.5%	0.988	16.4%
VIS	0.913	0.962	0.991	17.1%	0.993	13.4%
FPC	0.945	0.964	0.945	19.4%	0.972	17.5%
LAN	0.961	0.956	0.970	18.1%	0.985	14.9%
DMN	0.982	0.980	0.987	19.2%	0.993	14.4%
Mean	0.929	0.954	0.970	19.5%	0.982	17.1%

 Table 3.4. RSN classification performance for alternative methodologies.

LP: Linear Projection; DR: dual regression; LDA: linear discriminant analysis; MLP: multi-layer perceptron. Data from the Optimization group (one correlation map per ROI per subject) were transformed by each method (Appendix B) to produce 7 RSN estimates per map. ROC analysis was performed to compute classification performance for each method. The differences between the RSN estimates and their ideal labels ($d_o \in \{0,1\}$) were used to compute RMS error for LDA and MLP methods.

To illustrate the statistical covariance of RSN estimates, ROIs were plotted in planes defined by pairs of RSN scores (Figure 9B, top row). SMN ROIs (cyan cluster) achieved the highest score along the SMN axis in the SMN vs. VIS plane, and likewise for VIS ROIs. In plots for DR and LDA, DAN ROIs achieved relatively high scores in both dimensions (dark blue cluster in quadrant 1). This observation corresponds to the moderate spatial overlap between DAN, VIS, and SMN in DR results in Fig. 9A. SMN (cyan) and VIS (green) vectors extend from the median score to the center of mass of the ROI clusters. These vectors form an acute angle in the DR results, corresponding to generally correlated SMN vs. VIS estimates of network identity. LDA separates these vectors by a larger angle, which corresponds to less VIS-SMN spatial overlap. However, the DAN ROIs still achieve a high score on the VIS and SMN axes; the significant overlap of the DAN and SMN clusters corresponds to the spatial overlap of the DAN and SMN topographies in Fig. 9A.

In contrast, MLP showed greater within-network scores and lower across-network scores. For example, SMN and VIS ROIs achieved values near unity along their respective axes, while ROIs from other networks, notably DAN, achieved values closer to the median score. MLP output scores across anti-correlated networks also were closer to the median score. As might be expected, the contrast between MLP vs. either LDA or DR was especially marked in the case of difficult to separate RSNs, specifically, LAN vs. VAN and LAN vs. DMN.

Estimates of RSN identity were generally more correlated for DR and LDA methods than MLP. The Pearson correlation coefficient was computed (across all ROIs) for every pair of RSN classes, to generate inter-class correlation matrices in Figure 9C. The DR-derived inter-class correlation (Fig. 9C) retained more of the structure evident in Fig. 3B than the MLP-derived result. The magnitude of inter-class correlation was smaller for the MLP method than for either DR or LDA (p<0.05 and p<10⁻⁵, respectively, Mann-Whitney U-test), indicating that the MLP produced more orthogonal estimates of RSN membership than the other methods. Overall, classification performance was higher for the MLP (0.982 AUC) than for DR (0.954) and LDA (0.970).

3.4 Discussion

The perceptron in this study was trained to associate functional connectivity patterns (correlation maps) with 7 discrete RSNs. This number of RSNs corresponds to one particular scale of

correlation structure of intrinsic human spontaneous fMRI activity (Lee et al., 2012; Yeo et al., 2011). After training, the perceptron recognized new correlation maps based on features of RSNs learned from the training data. Our results exploit the ability of the perceptron to operate outside the training data to generate voxel-wise estimates of network identity throughout the brain in individuals.

There are two primary measures of performance in this study. ROC analysis determines MLP performance as a classifier in the winner-take-all sense, i.e., categorical membership under the assumption that brain regions belong to a single RSN. RMS error indicates MLP performance as a regressor by measuring the deviation of a particular result from the ideal model of categorical membership. It is possible for the MLP to achieve perfect classification (AUC of unity) even when RMS error is far from zero. In fact, this is approximately what we found (Table 3.3). This result supports a view of the brain in which a given region may belong to multiple RSNs.

3.4.1 Inter-individual variability of MLP outputs

The present results (Figures 5-7) exhibit a high degree of face validity with respect to the training data and previously reported RSN results. Thus, for example, components of the DMN used as seeds to generate the training data were classified as DMN in all participants. This was true not only for easily classified networks (e.g., the DMN) but also for networks (e.g., VAN and LAN) that are inconsistently found by unsupervised procedures. The results shown in Figure 5 illustrate that the perceptron reliably classified RSNs in each individual in the Validation 1 group (0.984 worst case AUC), even in cases in which the RMS error was relatively high (> 0.175).

Analysis of voxelwise RSN membership estimates across a large cohort (100 subjects from Validation dataset 2) revealed RSN-specific zones of high as well as low inter-individual variability (Fig. 7, middle row). Voxels with high RSN scores generally showed the least intersubject variability. Such regions, e.g., the posterior parietal component of the DMN (Fig. 7, right column), were surrounded by zones of high variability (e.g., a ring around the angular gyrus). The pre-and post-central gyri consistently showed high SMN RSN scores but were bordered by regions of high inter-subject SMN variability. Interestingly, inter-subject variability was low also in areas with RSN scores near 0, particularly in areas typically anticorrelated with other networks (e.g., low DAN variance in the angular gyrus, a component of the DMN; low DMN variance in MT+, a component of the DAN) (Fox et al., 2006).

At least four factors potentially contribute to observed inter-subject MLP output variability: (i) limited or compromised fMRI data; (ii) limitations intrinsic to the MLP; (iii) differences in RSN topography attributable to anatomic variability; (iv) true differences in RSN topography independent of variable gyral anatomy. We consider each of the possibilities in turn. (i) The fMRI data used in the present work were obtained in healthy, cooperative young adults. Hence, the fraction of frames excluded because of head motion (Power et al., 2012) was low (about 4%). The total quantity of fMRI data acquired in each individual was generous by current standards (Van Dijk et al., 2010). However, fMRI data quantity clearly affects MLP performance (see section 4.5.2 below and Figure 10A). Current results suggest that more data generally improves MLP performance. The requirements for fMRI data quality and quantity for acceptable MLP performance in clinical applications remains to be determined. (ii) High variability in RSN boundary regions (e.g., Fig. 7, DMN, middle row) may reflect uncertainty attributable to multiple RSN membership, i.e., voxels with high "participation coefficients" (Guimera and Amaral, 2005; Power et al., 2011). Voxels with multiple RSN membership may be more difficult to classify because the training data included only maps derived from seeds assigned to single networks.

(iii) Figure 6 indicates that the MLP captures a substantial portion of anatomic variability. However, some part of MLP mapping imprecision may be explained by uncorrected anatomical variability. To investigate this possibility, we compared the overall RSN standard deviation map (Fig. S3A) to sulcal depth variability (Fig. S3B) and found a weak spatial correlation (r = 0.2). By inspection, these maps were concordant only at a broad spatial scale: both showed low variability in primary motor/auditory/insular cortices and high variability elsewhere. Little correspondence was evident at finer scales (note lack of annular patterns in Fig. 3.S3B). The degree to which anatomical variability contributes to spurious variance in RSN topography estimates may be addressed by measuring the degree to which non-linear or surface-based registration decreases inter-subject variance and increases overall MLP performance (higher AUC, lower RMS error).

(iv) On the other hand, inter-individual differences may reflect "true" individual variability in RSN topography independent of gyral anatomy (Mueller et al., 2013). Previous work has demonstrated that inter-individual differences in task-evoked activity correspond to "transition zones" in resting state networks (e.g., the boundary between parietal DMN and DAN regions) (Mennes et al., 2010). These same regions appear in our inter-subject variance maps for both DMN and DAN (Fig. 7). We also note that areas of high RSN score variability (pre-frontal, parietal, lateral temporal) broadly correspond to regions exhibiting the greatest expansion over the course of human development and evolution (Hill et al., 2010). This correspondence may be coincidental, but it is consistent with the hypothesis that later developing or evolutionarily more recent areas of the brain tend to be more variable across individuals.

In summary, there are many potential contributions to observed RSN topographic variability. Because we did not use non-linear volume registration in this work, Fig. 3.6 retains individual differences in gyral anatomy. By inspection, the MLP was able to track these differences. Thus, it is reasonable to expect that the MLP will find "true" differences in RSN topography not attributable to variable gyral anatomy. Future studies are needed to compare MLP-derived topographies with, e.g., task-evoked responses, after correcting for anatomical variability.

3.4.2 External Validity and Generalizability

Two distinct types of external validity, that is, correct classification outside the Training set (areas covered by the seed ROIs), are evident in our results. First, high overall MLP performance was achieved for *a priori* seed-based correlation maps in the Optimization (98.2% AUC) and Validation 1 datasets (98.8% AUC). Performance was reliable in all participants (97.1% worst-case AUC), which is critical in clinical applications. Second, and perhaps of greater scientific interest, the RSN estimates in areas not covered by seed regions were strongly concordant with previously reported task-based and resting-state fMRI results. For example, while no temporal FPC seed ROI was included in the training set, a posterior temporal gyrus locus was classified as FPC (Lee et al., 2012; Power et al., 2011; Yeo et al., 2011) at the group
level (Fig. 3.7, FPC column). Similarly, the MLP also identified the parahippocampal gyrus as DMN (Kahn et al., 2008).

The MLP identified as LAN components of dorsal and ventral streams previously associated with cortical speech processing (Hickok and Poeppel, 2004) see also (Binder et al., 2011). Whereas the ventral components were bilateral, the dorsal components were left lateralized (Fig. 8, white arrow, LAN column) (Hickok and Poeppel, 2007). This finding represents a strong demonstration of external validity, as the left dorsal region was not included in the Training set. The right inferior cerebellum was first associated with language function by PET studies of semantic association tasks (Petersen et al., 1988). Identification of this region here as part of the LAN network (Fig. 8, WTA, Z = -30 and -47) is doubly significant: First, no cerebellar seeds were used to generate training data and cerebellar voxels were excluded from the gray matter mask; hence, these voxels were not seen by the MLP. Second, lateralized cerebellar RSN components typically are not found by unsupervised seed-based correlation mapping (Buckner et al., 2011).

These findings highlight the capabilities of supervised learning applied to the problem of identifying RSNs in individuals. The cortical representation of language (primarily Broca's and Wernicke's areas) has been extensively studied using task-based fMRI (Binder et al., 2011) and correlation mapping with *a priori* selected ROIs (Briganti et al., 2012; Hampson et al., 2006; Pravata et al., 2011; Tomasi and Volkow, 2012). However, the language network, as presently defined, typically is not recovered as such by unsupervised methods, e.g., (Power et al., 2011; Yeo et al., 2011). Rather, components of the LAN are generally found only at fine-scale RSN descriptions. Thus, an RSN including Broca's and Wernicke's areas appears as the 11th of 23

components in (Doucet et al., 2011); these same areas were identified as VAN by Power and colleagues (2011) and DMN by Yeo and colleagues (2011). Lee et al., (2012), found a component consistent with the presently defined LAN at a hierarchical level of 11 (but not 7) clusters. Thus, the present work demonstrates the potential of supervised learning to find networks that are subtle features of the BOLD correlation structure. These may be minor sub-components within hierarchically organized RSNs or functional entities of high scientific interest or clinical value that do not fit within a hierarchical organization, i.e., extend over multiple levels or across multiple branches.

Because the MLP is a universal function approximator, it is subject to over-fitting. Overfitting refers to learning features that are particular to the training set but that do not generalize to other sets. To minimize over-fitting, we halt training when Optimization dataset error reaches a minimum (Figure 4A). However, because early stopping is implemented throughout optimization by simulated annealing, over-fitting may still occur with respect to the Optimization dataset. Therefore, we demonstrate the performance of the fully trained MLP in two Validation datasets (Figs. 3.5-8).

3.4.3 Comparison of the MLP to dual regression (DR) and linear discriminant analysis (LDA)

The MLP, DR, and LDA all represent different strategies for extending RSN mapping results obtained at the group level to individuals. The MLP showed better spatial specificity of RSN estimates than either DR or LDA (Fig. 3.9A) and produced more orthogonal estimates of RSN identity in *a priori* ROIs (Fig. 3.9B). These comparative results indicate greater statistical

independence of RSN estimates obtained by the MLP. However, perfect separation of classes was not achieved by any method, as indicated by residual correlation of RSN estimates (non-zero off-diagonal elements in Fig. 3.9C). This residual was greatest in the least separable RSNs (compare Figs. 3.9C and 3.2B).

Performance differences across the three methods can be related to their underlying algebraic structures, which reveal interesting commonalities as well as differences (Appendix 3.B). All three methods operate by transforming individual voxel-wise covariance or correlation matrices into 7 dimensional RSN membership estimates at each voxel. However, the methods differ in the strategies used to achieve separation of RSN estimates. LDA requires considerable dimensionality reduction by PCA preprocessing. The optimal number of PCs was found to be 20, but this accounted for only 70% of the variance. In contrast, the MLP does not strictly require PCA preprocessing although this step greatly reduces the computational load without sacrificing information. In fact, the MLP performance optimum was obtained with 2,500 PCs (Figure S2), which included 99.97% of the variance. DR, as conventionally implemented (Zuo et al., 2010), does not involve PCA preprocessing or training.

Both LDA and MLP optimize separation of classes using thousands of labeled training samples, which captures variability across brain regions and individuals. Therefore, the superior performance of the MLP is not simply attributable to a large number of training samples. Rather, high-dimensional non-linear classification boundaries allow the MLP to extract arbitrary features from a large (2,500 PCs) input space. Future work will compare the MLP to LDA and DR in patients with focal lesions, i.e., stroke or brain tumors. At issue is performance under circumstances in which RSNs exhibit altered topography.

3.4.4 Dynamics of perceptron training reflect hierarchical brain organization

Several studies have demonstrated that resting state networks are hierarchically organized (Boly et al., 2012; Cordes et al., 2002; Doucet et al., 2011; Lee et al., 2012; Marrelec et al., 2008). Here, the hierarchical scale of an RSN is reflected in training performance trajectories (Fig. 4B): the DMN was the first to be separated from other RSNs. The DMN arguably is the most robust feature in the correlation structure of intrinsic brain activity. Its topography is very similar across RSN mapping strategies, specifically, spatial ICA (Beckmann et al., 2005) and seed-based correlation mapping (Yeo et al., 2011). Here, the DMN and regions anti-correlated with the DMN (Fox et al., 2005) were well separated along the first principal component of the training data (Figure 3)¹.

After the DMN, the sensorimotor and visual networks were next to achieve separation (Fig. 4B). These networks are often seen at the next level down in the RSN hierarchy as offshoots of the anti-DMN (Lee et al., 2012) or 'extrinsic system' (Doucet et al., 2011). The DAN achieved only a small peak in error descent compared to other 'extrinsic' networks, although this occurred in close proximity to SMN and VIS. In contrast, the LAN and VAN were last to achieve separation. This corresponds to the observation that LAN and VAN systems are typically found by analyses extending to lower levels of the RSN hierarchy (Lee et al., 2012; Power et al., 2011).

¹ Various labels, viz., "task-positive"/"task-negative" (Fox et al., 2005) and "intrinsic"/"extrinsic" (Doucet et al., 2011) have been attached to the DMN/anti-DMN dichotomy (for a critique of this nomenclature see Spreng, R.N., 2012. The fallacy of a "task-negative" network. Frontiers in psychology 3, 145.). However, these labels refer to the cognitive operations putatively represented in functional systems, which topic is outside the scope of the present work.



Figure 3.10. Examples of Objective Evaluation of Methodology.

A. Effect of total quantity of fMRI data on MLP performance. The plotted points (small triangles) represent total RMS error obtained with the fully trained MLP under three random subsamplings of the Validation 1 dataset. RMS error (E) was fit to a 3-parameter rational function (red line). Asymptotic RMS error (~15.6%) was estimated from the function model. Note monotonically decreasing error with increasing data quantity. The large symbols report values for particular datasets: diamond: Training; circle: Optimization; triangle: Validation 1; square: Validation 2. The inset surface displays show the effect of available data quantity on WTA results. Note less RSN fragmentation with more data. B. Effect of Optimization ROI size on MLP performance. Each seed radius was evaluated with 5 replicates. Red line: locally linear scatterplot smoothing (LOESS, smoothing parameter of 0.5). Note clear minimum at approximately 10 mm radius.

3.4.5 MLP performance applied to the evaluation of fMRI methodology

3.4.5.1 Objective assessment of image quality

Modern imaging theory defines image quality as the capacity to enable an observer to perform a

specific task (Barrett et al., 1998; Kupinski et al., 2003). Here, the observer is a multi-layer

perceptron and the task is to assign RSN values (or labels) to each voxel. Performance is

evaluated in terms of mean squared error and ROC analysis. It follows that MLP performance

can be used to evaluate image quality across a wide range of variables, e.g., scanners, and

acquisition parameters (repetition time, run length, resolution), preprocessing strategies (nuisance regression, filtering, spatial smoothing) and data representations (surface or volume based). We demonstrate this principle by systematically evaluating MLP performance in relation to quantity of fMRI data and seed ROI size.

3.4.5.2 Quantity of fMRI data

The relation between total quantity of fMRI data and MLP performance is shown in Figure 10A. The plotted points represent three random resamplings of all data in the Validation 1 dataset. RMS error as a function of data quantity was well fit ($r^2=0.994$) by a three-parameter empirically derived rational function. The parameterized function implies that output RMS error monotonically decreases with increasing total fMRI data length but ultimately asymptotes at ~15.6%. The biological significance of this asymptote is discussed below (Section 3.4.6).

3.4.5.3 Optimal seed ROI size

The relationship between seed ROI radius and RMS error was explored using the optimal MLP architecture (2,500 PCs, 22 hidden nodes) determined with 5 mm radius seeds. All seeds were masked to include only gray matter voxels. The results of systematically varying seed ROI size are shown in Figure 10B. A clear minimum in RMS error was obtained with seeds of approximately 10.5 mm radius. Voxel-wise RSN topographies were qualitatively similar across ROI sizes, but larger seeds generated less noisy RSNs with more pronounced peaks. This result is unexpected, as it deviates from the current standard practice of using approximately 6 mm radius seeds (e.g., (Marrelec and Fransson, 2011)). There are several possible explanations for this result. Large seeds may best match the characteristic dimensions of RSNs in the 7-network

level description of the brain. Alternatively, large seeds may compensate for mis-registration in affine-coregistered, volume-preprocessed data. We anticipate that smaller seeds will be optimal when estimating RSN membership of surface-coregistered, geodesically smoothed data. Hence, the results shown in Figure 3.10B should not be interpreted as unambiguously indicating that 10.5 mm radius seeds are optimal for correlation mapping in general. Rather, the large optimal radius (10.5 mm) indicates that averaging over more voxels outweighs loss of spatial specificity in this paradigm. Alternatively, the resultant increase in blurring may have corrupted the training data, which can lead to a more robust classifier (Dunmur and Wallace, 1993).

3.4.6 Limitations

The present MLP results were obtained using a particular set of RSNs selected for their scientific and clinical value in the context of ongoing research. A different training set including other RSNs might be optimal in other circumstances. MLP performance may be expected to vary with the number and separability of RSNs being classified as well as the total duration (Fig. 10A) and quality of acquired resting state fMRI data.

As discussed above (section 3.4.1), inter-individual differences in computed RSN topographies may reflect multiple factors. Cross-gyral contamination due to the relatively large voxels used in this study (3-4 mm acquisition, 3 mm post-processing analyses) may limit the precision of RSN estimation in our dataset (see (Yeo et al., 2011) for a discussion of this issue). Of greater theoretical importance is that we cannot distinguish between correctly identified geodesic (parallel to the cortical surface) shifts of RSN topography versus morphological differences in gyral/sulcal anatomy. Potential strategies for validating MLP-derived results

individuals include comparison with measures of structural connectivity (Damoiseaux and Greicius, 2009) and invasive electrophysiologic recording (He et al., 2008).

As shown in Figure 3B as well as in prior work (Boly et al., 2012; Doucet et al., 2011; Lee et al., 2012; Marrelec et al., 2008), RSNs are hierarchically organized. Thus, a major dichotomy separates the 'extrinsic' (DAN, VAN, VIS, SMN) from 'intrinsic' networks (FPC, LAN, DMN). At the next level of granularity, RSN blocks are distinguishable within the major dichotomy. However, the cognitive domains corresponding to these RSNs (e.g., 'motor', 'language', 'attention', etc.) are not conventionally regarded as hierarchically organized. Our training labels are categorical because they were generated from task-fMRI responses corresponding to conventionally understood cognitive domains (see Table 3.2). Thus, this work is fundamentally limited in that we impose a 'flat' conceptualization of brain function onto an intrinsically hierarchical system. This is reflected in the fact that ROIs are almost perfectly classified (by the AUC measure) in all datasets, yet RMS error always remains substantial (15%-20%) (Table 3.3, Fig. 10A). The existence of this residual may indicate that resting-state brain networks are inherently non-separable in the sense of classification. Indeed, this is consistent with the notion of "near decomposability" of hierarchical systems formed by multiple, sparsely inter-connected modules (Simon, 1995); this concept has been extended to brain networks (Meunier et al., 2010).

Another potential limitation is that all present analyses assume temporal stationarity, as do the overwhelming majority of extant papers on intrinsic BOLD activity. However, a growing literature (Chang and Glover, 2011; Kiviniemi et al 2011; Hutchinson et al 2012; Allen et al 2012) indicates that resting state correlation patterns fluctuate on a time scale of minutes. Our analysis of the effect on classifier performance of varying the total quantity of fMRI data (Fig. 10A) utilized contiguous epochs to the extent possible given fMRI runs of duration ~5 minutes. Less data reliably yielded worse performance. This result may be attributable either to sampling error (i.e., limited signal to noise ratio) or true temporal non-stationarities or both. Similarly, the performance floor may reflect non-stationarities. Disambiguating these possibilities would require much longer contiguous acquisitions.

3.4.7 Summary

The MLP estimates RSN membership at the voxel level via computed correlation maps. After training, it reliably identifies RSN topographies in individuals. RSN estimation is rapid (2 minutes using Matlab running on Intel i7 processors) and automated, hence suitable for

deployment in clinical environments. After training, operation is independent of any particular seed. Therefore, the trained MLP is expected to be robust to anatomical shifts and distortions, for example, owing to enlarged ventricles and mass effects or even loss of neural tissue (e.g., stroke).

In this work, the MLP was trained to operate in 3D image space for compatibility with clinical imaging formats. However, the MLP concept can be readily adapted to operate on correlation maps represented on the cortical surface. Similarly, an MLP can be trained to ignore anatomical abnormalities (e.g., brain tumors) by altering the domain of the training set, i.e., excluding tumor voxels. This possibility will be explored in future work.

3.5 References

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Appendix 3.A: Multi-layer Perceptron Training Algorithm

The input to the MLP algorithm consists of correlation maps projected onto eigenvectors

computed by PCA preprocessing of the training data (see main text section 2.4.1). Each input's

loadings onto the *i*-th eigenvector, y_i , is formally defined as the output value of the *i*-th input

layer node. This corresponds to the first layer in Fig. A1.

The total input to a hidden or output layer node, v_h or v_o , respectively, is computed as the sum of all output values from the previous layer weighted by feed-forward connections:

$$v_h = \sum_{i=1}^{2500} y_i \cdot w_{hi}$$

$$v_o = \sum_{h=1}^{22} y_h \cdot w_{oh}$$
(A.1)

where *i*, *h*, and *o* index input, hidden, and output nodes; y_h indicates the output value received from hidden layer node *h*; w_{hi} indicates the connection weights from input node *i* to hidden layer node *h*, and similarly for hidden to output layer connections w_{oh} . In this work, connection weights were initialized by sampling values from a uniform distribution over the interval [-0.01, 0.01].

Total inputs to each node are transformed into output values by layer-specific activation functions, φ_h and φ_o , which are the hyperbolic tangent and logistic curves, respectively:

$$y_{h} = \boldsymbol{\varphi}_{h}(v_{h}) = \tanh(b \cdot v_{h})$$

$$y_{o} = \boldsymbol{\varphi}_{o}(v_{o}) = (1 + e^{-v_{o}})^{-1},$$
(A.2)

where b = 0.1. The hidden node index, h, ranges from 1 to 22. The output node index, o, ranges from 1 to 8.

The overall transfer function of the perceptron is given in Eq. (A.3). This formula represents the propagation of inputs through the MLP (Figure A1):

$$y_o = \boldsymbol{\varphi}_o \left(\sum_h \boldsymbol{\varphi}_h \left(\sum_i y_i \cdot w_{hi} \right) \cdot w_{oh} \right)$$
(A.3)



Figure 3.A1. Standard Multi-layer Perceptron Architecture.

This perceptron assigns RSN labels to input spatial BOLD patterns represented in PCA space (forward pass). The input nodes (y_i) take on values from the principal components of the input image. v: summed inputs to a layer (Eq. (A.1)); φ_h : hyperbolic tangent activation function (Eq. (A.2)); φ_o : logistic activation function (Eq. (A.2)). Output values of the perceptron (y_o , Eq. (A.3)) are compared to training labels corresponding to the assigned RSN (d_o) to produce an error signal (e_o) which, in turn, is used to update the connection weights, ($w_{i,h}$, $w_{h,o}$, Eqs. (A.4)-(A.7)). Layers are fully connected (all-to-all), although only adjacent incoming/outgoing connections are illustrated.

After propagation of the input data, the output value for each node, y_o , is compared to

the *a priori* RSN output labels, $d_o \in \{0,1\}$, to find the error $(e_o = d_o - y_o)$. The total squared error, summed across all output nodes and all training samples, is given by *E*. The local gradient of the total error at output node *o* is computed as:

$$\boldsymbol{\delta}_{o} = \frac{dE}{dv_{o}} = \frac{dE}{dy_{o}} \frac{dy_{o}}{dv_{o}} = -e_{o} \cdot \boldsymbol{\varphi}_{o}' \left(\sum_{h} y_{h} \cdot w_{ho}\right), \tag{A.4}$$

where the prime notation indicates the first derivative of φ_o (see application of chain rule in Eq. 4 in (Rumelhart et al., 1986)). Note that the derivative of the input, v_o , with respect to the

weights, w_{oh} , in Eq. (A.1) is simply the output from the previous layer, y_h . The chain rule can therefore be used to calculate how total error changes with respect to the weights, i.e.,

 $\frac{dE}{dw_{ob}} = \frac{dE}{dv_o} \cdot \frac{dv_o}{dw_{ob}} = \boldsymbol{\delta}_o \cdot \boldsymbol{y}_h$. This gradient can thus be used to adjust the connection weights:

$$w_{oh}(k+1) = w_{oh}(k) - \boldsymbol{\eta}(k) \cdot \boldsymbol{\delta}_{o}(k) \cdot y_{h}(k), \qquad (A.5)$$

where η is the instantaneous learning rate (see Eq. (A.9) below and Fig. A2) and *k* is the iteration index.



Figure 3.A2. Learning rate (η) dependence on iteration index.

The initial learning rate was small $(\eta(0) = A = 5 \cdot 10^{-4})$ to allow the MLP to begin a gentle descent in error gradient towards a stable solution. The learning rate increased exponentially (B = -3, M = 2.5), until saturating at an empirically determined upper limit of stability $(K = 2 \cdot 10^{-3})$.

The weights to the hidden layer from the input layer are similarly adjusted:

$$w_{hi}(k+1) = w_{hi}(k) - \boldsymbol{\eta}(k) \cdot \boldsymbol{\delta}_{h}(k) \cdot y_{i}(k)$$
(A.6)

However, the local gradient of the error at hidden node h, δ_h , must be computed indirectly by back-propagation of the local gradient of error at the output layer, weighted by the connections between the hidden and output layers:

$$\boldsymbol{\delta}_{h} = \frac{dE}{dv_{h}} = -\boldsymbol{\varphi}_{h}' \left(\sum_{i} w_{hi} \cdot y_{i} \right) \cdot \sum_{o} \boldsymbol{\delta}_{o} \cdot w_{oh}$$
(A.7)

The present results were obtained using an empirically determined learning rate parameter schedule, $\eta(k)$, which depended on the iteration index, k. The range of η values yielding stable learning was determined, where instability was defined as divergence or oscillation of classifier weights or output values. The learning rate schedule adaptively increased as a sigmoid in log iteration index (Fig. A2):

$$\eta(k) = A + \frac{K - A}{1 + e^{-B(\log_{10} k - M)}}$$
(A.8)

Thus, $A = 5 \cdot 10^{-4} = \eta(0)$ was the initial learning rate and $K = 2 \cdot 10^{-3} = \eta(\infty)$ the

maximal rate; B = -3; M = 2.5. The presently reported η values provided stable learning with double precision computations for the final architecture described in this work. Architectures with larger weight matrices required smaller values of η .



Figure 3.A3. MLP Output Values over the Course of Training. A,B,C: Each plot represents the value of a particular output node; each trace represents a particular training input (single correlation map). Traces are colored according to training labels. All output node values are initially approximately 0.5 and later increase during training.

Significant separation of the DMN from other networks in the Training (A) and Optimization (B) datasets began at approximately 10 iterations. Maximal separation was achieved at ~1000 iterations in the Optimization dataset (B). The LAN achieved separation considerably later (C). Training trajectories for RSNs are shown in main text Figure 4.

Appendix 3.B: Algebraic Comparison of Methods

This appendix describes the algebraic relationship between dual regression (DR), linear discriminant analysis (LDA), and the multi-layer perceptron (MLP). We demonstrate that all three methods act on the second-order statistics over voxel pairs (covariance for DR and correlation and for LDA and MLP). Each method computes subject-level descriptions of group-defined spatial components.

3.B.1 Definitons

Let B_i be the BOLD volumetric timeseries (voxels × time) for subject *i* after preprocessing and masking to include only grey matter voxels. The voxel-wise temporal covariance matrix is $B_i B_i^T$, where the superscript *T* indicates the matrix transpose. Similarly, the voxel-wise correlation matrix is $b_i b_i^T$, where *b* is the volumetric timeseries after normalizing each voxel to unit variance. Let *A* be the matrix of group-defined RSN maps (voxels × components).

3.B.2 Linear Projection (LP)

Projecting voxel-wise covariance maps onto group-defined components is algebraically the simplest possible method for extending group results to individuals (Eq. (B.1)).

$$A_i = B_i B_i^T A \tag{B.1}$$

Eq. (B.1) generates individual, voxel-wise RSN scores for each group-derived component. We do not report such maps. However, we do evaluate nearest neighbor LP performance in comparison to DR, LDA, and MLP (main text Table 3.4). To perform this comparison in a manner comparable across methods, covariance maps were generated for all *a priori* seeds in all Optimization participants. These maps were projected directly onto the group-defined RSN components. The resulting scores, i.e., the inner products of each seed-based covariance map with each group-derived RSN component, were used to perform nearest-neighbor classification.

3.B.3 Dual Regression

Dual regression generally is used to extend group-defined results derived by group sICA to individuals (Zuo et al., 2010). The first step of dual regression assumes a representation of the BOLD timeseries as a linear model of fixed group-level RSN components, A (voxels × components), each evolving over an associated timecourse in T_i (components × time),

$$B_i = AT_i + \varepsilon_i, \tag{B.2}$$

with some error $\boldsymbol{\varepsilon}_i$. Note that for comparison to our work, A was computed as averaged seedbased correlation maps rather than independent components; nevertheless A has full column rank and $A^T A$ is invertible. Therefore, the left pseudoinverse can be used to find the least squares solution for the system of RSN timecourses specific to each individual:

$$T_i = A_L^+ B_i \tag{B.3}$$

where $A_L^+ = [A^T A]^{-1} A^T$ is the *left* Moore-Penrose pseudoinverse of A. It may be noted that group sICA generates spatially orthogonal components $(A^T A \propto I)$, in which case $(A_L^+ \propto A^T)$.

However, in our work, the training set of RSNs is only approximately orthogonal. The second step of dual regression solves for the subject-specific RSN topographies best described by the timeseries recovered in step 1:

$$A_{i} = B_{i}T_{iR}^{+} = B_{i}\left(A^{+}B_{i}\right)^{+}$$
(B.4)

where $T_{iR}^{+} = T_i^T [T_i T_i^T]^{-1}$ indicates a *right* pseudoinverse of T_i . Note, $T_i T_i^T$ is invertible because T_i has full row rank. Combining Eqs. (B.2) and (B.3) yields

$$A_{i} = B_{i} \left(A^{+} B_{i} \right)^{T} \left(\left(A^{+} B_{i} \right) \left(A^{+} B_{i} \right)^{T} \right)^{-1}$$

$$= B_{i} B_{i}^{T} A^{+T} \left(T_{i} T_{i}^{T} \right)^{-1}$$
(B.5)

Thus, dual regression computes group-defined RSN topographies in individual *i* as a linear transformation on the voxel-wise covariance matrix, $B_i B_i^T$. To evaluate DR classification, the quantities necessary to define the final algebraic form of dual regression, i.e., A^{+T} and $(T_i T_i^T)^{-1}$ in Eq. (B.5), were first computed for each participant. Seed-based covariance maps then were generated for all ROIs and all participants and inner products with $A^{+T} (T_i T_i^T)^{-1}$ were computed to obtain RSN scores for each ROI in each individual.

3.B.4 PCA/LDA:

Linear discriminant analysis (LDA) was first described in 1936 (Fisher, 1936). Briefly, this method computes discriminant vectors that are the basis for a reduced space (of dimensionality equal to the size of the feature space) in which the between-class vs. within-class separation has been maximized across training data. LDA preceded by input feature space dimensionality reduction using principal components analysis (PCA) is well known, e.g., (Lyons et al., 1999). Here, PCA-LDA was implemented using the same input data and training labels as for the MLP method, except that 20 principal components gave optimal performance with PCA-LDA whereas 2500 components was optimal with MLP. After training, PCA-transformed voxelwise correlation maps ($b_i b_i^T W_{PCA}^{20}$) were projected onto the discriminant vectors (W_{LDA}) to produce subject-specific RSN topographies:

$$A_i = b_i b_i^T W_{PCA}^{20} W_{LDA} \tag{B.6}$$

3.B.5 PCA/MLP:

The following formulation of the forward pass is simply Eq. (A.3) converted to matrix form, using the PCA-transformed voxel-wise correlation maps $(b_i b_i^T W_{PCA}^{2500})$ as the input.

$$\boldsymbol{A}_{i} = \boldsymbol{\varphi}_{o} \left(\boldsymbol{\varphi}_{h} \left(\boldsymbol{b}_{i} \boldsymbol{b}_{i}^{T} \boldsymbol{W}_{PCA}^{2500} \boldsymbol{W}_{1} \right) \boldsymbol{W}_{2} \right)$$
(B.7)

Where W_1 and W_2 are matrix forms of the weights between the input and hidden, and the hidden and output layers, respectively.

3.B.6 Comment:

DR, LDA and MLP all compute individual RSN topographies (A_i) by algebraic

transformation of observed individual second order voxel-wise statistics, i.e., $B_i B_i^T$, or $b_i b_i^T$. Several differences between the methods are evident in Eqs. (B.5)-(B.7):

• LDA and DR involve strictly linear operations whereas the MLP includes nonlinear activating functions $(\boldsymbol{\varphi}_{h}, \boldsymbol{\varphi}_{o})$.

• The dimensionality of the LDA vs. MLP weight matrices is very different: W_{LDA} is 20 × 7 whereas W_1 is 2500 × 22 and W_2 is 22 × 7. Thus, compared to LDA, the MLP has many more connection weights available for optimization.

• All three methods project $B_i B_i^T$ or $b_i b_i^T$ onto weight matrices. This operation amounts to computing the inner product of an individual's covariance/correlation matrix times a set of RSN-specific templates. In fact, to the extent that sICA-derived templates are spatially orthogonal $(A^T A \propto I)$, the first factor in Eq. (B.5) reduces to a simple projection of $B_i B_i^T$ onto A, which is equivalent to nearest neighbor classification, i.e., Eq. (B.1).

• The last factor in Eq. (B.5), $(T_i T_i^T)^{-1}$, compensates for non-orthogonality of RSN time courses in each individual. This "unmixing" operation in DR occurs is a space of dimensionality equal to the number of RSNs (7 in this work). In LDA, "unmixing" is performed in a larger feature space (20 dimensions). Interestingly, while the MLP extracts features from a very high dimensional space, the optimal number extracted features ($N_h = 22$) was close to the optimal LDA input dimensionality. LDA, a operating with a simple linear transform, required a heavily truncated space for optimal performance. The optimal dimensionality, 20 PCs accounted for 70.4% of the variance of correlation topographies with 0.6% of variance in the 20th component. The optimal space for the MLP method accounted for 99.98% of the variance, including components of very small variance $(2.7 \cdot 10^{-7} \text{ for the } 2500 \text{th}, 99.98\%$ accounted in total) in the training data. Performance differences indicate that the MLP more efficiently selects from a larger set of features (much of which can be noise) with which to model arbitrary relationships and thus approximates a smooth boundary. LDA must perform a harsh truncation because of the amplification of noise caused by small components. These PCA maneuvers are not applicable to conventional dual-regression (Zuo et al., 2010), which does not explicitly compute the covariance matrix. However, regularization and smoothing steps theoretically could be performed on the raw BOLD data, B_i , using ICA to exclude noise components from further analysis.

3.6 Supplemental Materials

Correction of odd/even slice intensity differences (banding)

Assume that odd and even slices are affected by alternating multiplicative intensity errors. Thus, for every voxel in an even slice, the measured intensity is $\tilde{v}_{ik} = v_{ik}(1 + \partial)$, where v_{ik} (always positive) is the unbiased (true) intensity and the subscript indexes voxel i in slice k. Similarly, in odd slices, the measured intensity is $\tilde{v}_{ik} = v_{ik}(1 - \partial)$. Thus, measured intensities on successive slices are biased in the opposite direction (banding). They key operational assumption is that the true intensity profile across slices is, on average, locally linear. Accordingly, the average measured intensity on the slices above and

below will differ from the current slice by $2s \partial v_{ik}$, where $s = (-1)^k$ depends on the parity of the slice index. Therefore, ignoring the difference between v_{ik} and \tilde{v}_{ik} , we have

$$(1/2)(\tilde{v}_{i(k+1)} + \tilde{v}_{i(k-1)}) - \tilde{v}_{ik} \gg 2s \partial \tilde{v}_{ik}$$
(S1)

To solve for ∂ , both sides of Eq. (S1.1) are weighted by \tilde{v}_{ik} , to emphasize bright voxels, and the resulting quantities are summed over the available data.

$$\partial = \frac{\partial \hat{e}(1/2)(\tilde{v}_{i(k+1)} + \tilde{v}_{i(k-1)}) - \tilde{v}_{ik} \hat{e}(-1)^{k} \tilde{v}_{ik}}{2 \partial_{i,k}^{\alpha} \tilde{v}_{ik}^{2}}$$
(S2)

It may be noted that banding is more marked during the first few volumes of each fMRI run, i.e., before achieving magnetization steady state. Having estimated ∂ , the measured data are corrected by inverting $\tilde{v}_{ik} = v_{ik}(1 + \partial)$.

The debanding algorithm was originally developed in 1995 to enable acquisition of interleaved fMRI data without slice gaps (Ojemann et al., 1997). On a 1.5T Siemens Vision scanner, which generated slice selection RF profiles using analog circuitry, the value of *a* in interleaved, 8mm slice fMRI data (after achieving magnetization steady state) typically was ~0.035. The corresponding figure for fMRI acquired on the Siemens 3T Allegra scanner (present data, 4mm slices), which has digital RF circuitry, is 0.007. This figure applies to temporally continuous fMRI, i.e., no delay between volumes (present Training and Optimization datasets; see main text Table 3.1). This small magnitude of banding artifact might be reasonably ignored, although we always apply the correction. However, introducing a 1 sec temporal delay between volumes (to enable simultaneous EEG recording without gradient switching

artifact; present Retest/Validation dataset) leads to substantial banding even in the steady state regime. The typical steady-state value of a in the Validation dataset is 0.09.

Meta-analysis of task fMRI and generation of training data

Task meta-analyses

The objective of this procedure is to isolate, in task-fMRI responses, canonical seed ROIs yielding consistent resting state correlation maps. To this end, seed ROIs were generated by metaanalyses of task-fMRI studies. Task-response foci were initially assigned to one of 10 functional networks, counting foveal and peripheral VIS as distinct (Table S1). Each task fMRI study contributed a variable number response foci. These foci were used as seeds to generate correlation maps in all 21 subjects in the Training set. The maps then were entered into random effects analyses (against the null hypothesis of no correlation) to produce Gaussianized t-statistic (Z-score) images. Z-score images representing seeds assigned to the same RSN were averaged. Additionally, a conjunction image representing at least 70% of random effects images for a given network (after thresholding at |Z| > 3) was produced. Averaged Z-score images were masked to include only voxels contained in the conjunction. Peaks of the conjunction-masked average were selected as center coordinates for 6mm spherical ROIs. Accordingly, we enforced the constraint that all ROIs must be separated by at least 12mm. This process resulted in a large set of ROIs that were operationally treated as provisional.



Figure 3.S1. ROIs in Volume Space.

Voxels contained within 6 mm spheres centered at each ROI coordinate are colored according to RSN assignment. Right hemisphere surface projections are shown in main text Figure 1.

Generation of MLP training data by iterative seed ROI refinement

The provisional ROI set was iteratively refined by maximizing the spatial concordance between the correlation map obtained from each seed vs. the map obtained by pooling all seeds within the RSN to which the seed was assigned. Pooled seed correlation maps were computed by averaging the time series across all seeds assigned to each RSN. The single seed and the pooled seed maps were averaged across subjects. RSN concordance was assessed as the spatial correlation between the (subject-averaged) single seed and the (subject-averaged) pooled seed maps. Seeds were considered outliers if their concordance estimate was less than 1.5 times the inter-quartile range below the median of all other seeds in the RSN. Outlier seeds were reassigned to the RSN of greatest concordance, unless they were maximally concordant with the currently assigned RSN, in which case they were removed. After reassignment and outlier rejection, new individual seed and pooled seed correlation maps were re-computed and the process was iterated. Convergence (no reassignments or outlier rejections) was achieved in 7 iterations. The cingulo-opercular (CO) network did not survive iterative refinement; most seeds were reassigned to the ventral attention network (VAN) or removed. Similarly, the auditory network (AN) was subsumed into the sensorimotor network (SMN) and the originally distinct foveal and peripheral visual networks were combined into a single (VIS) network.

Iterative refinement yielded 169 ROIs representing 7 RSNs with high intra- and low internetwork correlation (Figures 1 and S1). To these were added a nuisance category consisting of 6 ROIs in CSF spaces. The latter enabled the classifier to separate correlation patterns representing CSF vs. true RSNs. Computing correlation maps for each of the 175 seed regions in all 21 Training subjects produced 3,675 images that were used as training data. Each image in the Training set was masked to include only grey matter voxels, producing a 3,675 x 30,981 matrix. Similarly, $175 \cdot 17 = 2,975$ images were computed in the test data set. Each image was assigned to one RSN or CSF.

Supplemental Perceptron Training Methods

Architecture selection and ROI radius optimization

To optimize the number of input nodes, N_i , and hidden layer nodes, N_h , the perceptron was systematically trained over a dense sampling of architectures defined by the $(N_i \times N_h)$ plane. The optimal overall performance, defined as minimum RMS error, was found at 2,500 PCs and 22 hidden layer nodes (Fig. S2, red 'X'). The perceptron then was trained with this architecture using 10.5 mm radius ROIs. Lastly, the MLP weights were optimized through simulated annealing (see section 2.4.5 and Supplemental text Section S2.4.5), yielding an over-all classification performance of 0.9822 AUC with 17.1% RMS error (Test dataset). Without optimization by simulated annealing, overall performance for 50 training runs was 0.973 ± 0.001 AUC and 19.0% ± 0.2% RMS error (mean ± standard deviation) vs. 0.982 AUC and 17.1% RMS error after simulated annealing. Simulated annealing thus yielded a significant increase in RMS error ($p \sim 0$ by t-test). By inspection, RSN topographies after simulated annealing showed less high frequency speckle and better network specificity. Figure 10A illustrates a similar effect of decreasing RMS error.



Figure 3.S2. Search Space for Optimal Perceptron Architecture.

At logarithmically spaced samples in the $(N_i \times N_h)$ plane, the MLP was trained 8 times until reaching a minimum in RMS (see Fig. 4E). The quantity represented in the $(N_i \times N_h)$ plane is the minimum error over the 8 runs. The locus of the global minimum error (red 'X') defines an optimal architecture.

Simulated annealing details

Simulated annealing was implemented by randomly perturbing MLP weights. If the total error was thereby reduced, the perturbations were retained; otherwise the perturbations were discarded. Perturbation was achieved by multiplying each weight by a random multiplicative scalar, $N \hat{1} [0, \xi]$,

enforcing the condition that the expectation value of N^2 is unity, i.e., $E[N^2] = 1$. Algorithmically,

N = (1 - x)/(1 + x), where $x \mid [-1,1]$ is randomly sampled from a uniform distribution. "Cooling" refers to progressive narrowing of the range of N about unity. This was implemented by selecting the temperature, T, and restricting $x \mid [a, T]$, where a is such that $\hat{0}_{a}^{T}[(x - 1)/(x + 1)]^{2}dx = T - a$. Cooling was performed over K_{1} perturbation epochs and the entire annealing process was repeated K_{2} times. A geometric cooling function, $T(k_{1}, k_{2}) = T_{0}r^{(k_{1}+3k_{2})}$, generated progressively cooler temperatures over epochs (indexed by k_{1}) and repetitions (indexed by k_{2}). The following parameters were used: $r = 0.95; T_{0} = 0.4; K_{1} = 40; K_{2} = 20$. Thus, in the first perturbation of the first annealing, $N(40, 20) \mid [0.995, 1.005]$.





A. Inter-subject variability of RSN topography estimates evaluated in the combined Training and Optimization datasets (N=38). Normalized MLP output values were projected onto each subject's cortical surface. The standard deviation was computed across subjects for each network, and the result was averaged. B. Sulcal depth variability across the 38 subjects.

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Chapter 4: A Novel Data Driven Approach to Preoperative Mapping of Functional Cortex Using Resting State fMRI

Mitchell TJ, Hacker CD, Breshears JD, Szrama NP, Sharma M, Bundy DT, Pahwa M, Corbetta M, Snyder AZ, Shimony JS, Leuthardt EC. TJM, CDH, and AZS performed analyses for this study, which was written by TJM, CDH, and

ECL. JDB, NPS, MS, DTB, MP, MC, and JSS contributed to the methods, study design, revisions, and data acquisition for the acquisition for the project.

Abstract: Recent findings associated with resting state cortical networks have provided insight into the brain's organizational structure. In addition to their neuroscientific implications, the networks identified by resting state functional MRI (rs-fMRI) may prove useful for clinical brain mapping. Objective: To demonstrate that a data driven approach to analyze resting state networks is useful in identifying regions classically understood to be eloquent cortex as well as other functional networks. Methods: Study included six subjects undergoing surgical treatment for intractable epilepsy and seven subjects undergoing tumor resection. rs-fMRI data were obtained prior to surgery and seven canonical resting state networks (RSNs) were identified by an artificial neural network algorithm. Of these seven, the motor and language networks were then compared to electrocortical stimulation as the gold standard in the epilepsy patients. The sensitivity and specificity for identifying these eloquent sites was calculated at varying thresholds, which yielded receiver operating characteristic (ROC) curves and their associated area under the curve (AUC). RSN networks were plotted in the tumor subjects to observe RSN distortions in altered anatomy. Results: The algorithm robustly identified all networks in all subjects, including those with distorted anatomy. When all ECS positive sites were considered for motor and language, rs-fMRI had AUCs of 0.80 and 0.64, respectively. When the ECS positive sites were analyzed pairwise, rs-fMRI had AUCs of 0.89 and 0.76 for motor and language, respectively. Conclusion: A data driven approach to rs-fMRI may be a new and efficient method for pre-operative localization of numerous functional brain regions.

4.1 Introduction

An ongoing challenge in surgical resection of brain lesions is balancing the goal of maximizing resection with the need to preserve function. This is especially salient in the setting of epilepsy and glioma surgery where the lesions can be cortically based and intimately involved with eloquent regions. In both situations, resection around a seizure focus or maximizing tumor removal enhances clinical outcomes with regard to seizure freedom or survival, respectively (Keles et al., 2001, Lacroix et al., 2001, Keles et al., 2006, Sanai et al., 2008, McGirt et al., 2009, Hyun Kyung et al., 2010). The benefits of a larger resection, however, must be weighed against the cost of deficits incurred in areas of eloquent cortex, particularly in motor and language areas (Sanai et al., 2008). Because there is a high degree of individual variability in these areas, presurgical localization and intraoperative cortical mapping are often required to optimize the clinical outcome.

Functional magnetic resonance imaging (fMRI) has played an important role in the preoperative assessment of patients with lesions adjacent to eloquent cortex. fMRI measures neuronal activity using the ratio of oxyhemoglobin to deoxyhemoglobin as a contrast mechanism (known as Blood Oxygen Level Dependent, or BOLD, fMRI). In a typical block design application the subject alternates between a passive resting state and performing a task. Clinical applications of task-based fMRI have focused on localizing areas of critical function for presurgical planning (Matthews et al., 2006) and have been shown to correlate with intraoperative electrophysiology (Vlieger et al., 2004), Wada testing (Adcock et al., 2003), and prediction of loss-of-function post-operatively (Haberg et al., 2004). Despite its utility, taskbased fMRI has several disadvantages that limit its application for pre-operative functional localization. First, the results are dependent on how well the patient can perform the prescribed task. In the setting of a brain tumor, cooperation and effective participation may be impaired due to neurologic deficits or confusion (Pujol et al., 1998). Second, because the patient must be awake during the imaging procedure, sedation cannot be used. This often limits effective imaging in pediatric populations for whom conscious sedation is frequently necessary. Finally, task based fMRI can be lengthy if multiple functional sites are interrogated in a single imaging session.

As an alternative to task-based fMRI, resting state functional MRI (rs-fMRI) has been proposed as an imaging methodology for localizing critical sites independent of patient participation (Zhang et al., 2009). This approach uses the endogenous brain activity detectable with BOLD MRI to identify areas that are interacting at rest. Spontaneous BOLD fluctuations are low frequency (below 0.1Hz) oscillations in metabolic activity that are anatomically correlated within distinct functional networks (Fox and Raichle, 2007). First reported by Biswal et al., there is strong coherence which is reproducibly present between the left and right somatomotor cortices (Biswal et al., 1995, Fox et al., 2006b), between language areas (Cordes et al., 2000, Hampson et al., 2002), and between numerous other functional regions in the absence
of task performance. Using spontaneous activity, one can generate resting state correlation maps that are similar to the functional maps obtained from task activations (Smith et al., 2009). This approach has a number of advantages. Most importantly, patient participation is not required. An additional advantage is that these methods are robust; spontaneous fluctuations have been shown to persist under conditions of sleep (Fukunaga et al., 2006, He et al., 2008, Horovitz et al., 2009) and anesthesia (Kiviniemi et al., 2003, Peltier et al., 2005, Vincent et al., 2007, Breshears et al., 2012), as well as in the presence of tumors (Zhang et al., 2009). Thus resting state could potentially be widely applied irrespective of age and cognitive status. While holding substantial promise, these advanced techniques have not yet entered routine clinical practice due to the high level of technical support necessary to create these resting state maps. A common approach for network identification is the selection of a "seed region" in a characteristic location (such as the hand motor area to identify the somatomoter network). This approach can be biased by the selection of seed regions and is technically labor intensive. Often multiple regions are tested until the optimal network is identified. While this process is often successful in normal brains using standard atlas coordinates, it becomes more challenging in brains that are distorted due to disease (i.e. tumors and cortical dysplasia). Finally, rs-fMRI imaging has had limited comparison to the clinical gold standard of electrocortical stimulation (ECS).

In this study we evaluated the use of a novel methodology for identifying resting state networks with fMRI as a potential tool for preoperative imaging. Using a multilayer neural network technique, we have developed an approach that enables the identification of multiple functional networks from a single task independent data set. Moreover, these networks are identified automatically in a purely data driven approach independent of the need for an individual to pick seed regions. To assess the validity of the imaging findings as a potential clinical tool, language and motor networks were rigorously compared to the gold standard of ECS to localize essential eloquent cortex in patients suffering from epilepsy. Additionally, to assess the robustness of our technique in the presence of lesions, the technique was applied to seven patients with tumors. Taken together, these findings support the potential utility and augmented capability of rs-fMRI to enhance preoperative localization of functional regions.

4.2 Methods

4.2.1 Subjects

Six patients undergoing surgical treatment of intractable epilepsy and seven patients undergoing surgical resection of brain tumors participated in this study, which was approved by the Human Research and Protection Organization at Washington University School of Medicine (see Tables 4.1 and 4.2). Before inclusion, all patients gave written informed consent. With regard to the tumor subjects, seven participants who were screened as potential candidates for an awake craniotomy for tumor resection were included. All subjects had anatomic and rs-fMRI imaging prior to resection. Two underwent functional mapping with ECS. With regard to the epilepsy subjects, all participants had epileptic seizures refractory to treatment with antiepileptic medications and had previous documentation of epileptic seizures by video scalp electroencephalographic monitoring. All subjects were deemed candidates for invasive monitoring. Prior to surgical implantation of electrodes all subjects had anatomic and rs-fMRI imaging. Subjects underwent intracranial electrocorticographic monitoring to localize the epileptogenic zone of seizure onset and to perform functional mapping with ECS. Exclusion criteria included the presence of dysplastic cortex on clinical MRI. Each patient underwent an initial craniotomy for the subdural placement of an electrode array that was then removed with a second craniotomy approximately one week later during resection of the epileptic foci.

4.2.2 fMRI Analysis

All patients were scanned using a 3T TRIO Siemens scanner (Erlangen, Germany). rsfMRI data was acquired using a T2* EPI sequence (1x1x1 mm voxels; 128 volumes/run; TE=27 ms; TR=2s; FOV=256 mm; flip angle=90°) while the patients were instructed to remain still and fixate on a visual cross-hair without falling asleep. Anatomical imaging included T1-weighted magnetization prepared rapid acquisition gradient echo and a T2-weighted fast spin echo scan. All MR data was acquired in approximately 30 minutes for each patient. rs-fMRI data was preprocessed using the methods detailed in Zhang et al (Zhang et al., 2008).

rs-fMRI correlation maps were generated using a multilayer perceptron (MLP), an artificial neural network (Hacker et al., 2013). MLPs are supervised classifiers that are trained to map input data to pre-defined output classes using one or more hidden layers (Figure 4.1) (Rosenblatt, 1958, Rumelhart et al., 1986).



Figure 4.1. Voxel-wise classification of resting state networks (RSNs) using the multilayer perceptron (MLP) algorithm.

Voxel-wise correlation maps were obtained from resting state fMRI data and masked to include only grey matter voxels. The masked images were then passed into the MLP algorithm (see text), which produced RSN maps for the language (LAN), somatomotor (SMN), visual (VIS), dorsal attention network (DAN), ventral attention network (VAN), frontoparietal control (FPC), and default mode network (DMN).

In this work, the MLP was previously trained to associate correlation maps generated from canonical ROIs with a priori class labels corresponding to seven predefined resting state networks (RSNs) (Lee et al., 2012). The MLP consists of one input, hidden, and output node layer, fully connected in a feed-forward manner. Each training input was a correlation map (masked to include only gray matter voxels) generated from one of 169 canonical seed ROIs across 21 normal control subjects. Each node in a particular layer is connected to each node in the subsequent layer, and it is the strength, or weight, of these connections that allow the MLP to classify the input data. Thus, the input image is propagated through the layers of the MLP; the output was then compared to a seven dimensional binary output label vector (with a value of unity for the RSN to which the ROI is assigned, and zeros for the others). The difference of the output and the training label generated an error signal; the backpropagation algorithm (Rumelhart et al., 1986) was used to minimize the squared error across all RSNs for all correlation map training inputs. At each training iteration, performance on canonical ROIs was computed in a second 'optimization' dataset (N=17). Training was halted upon reaching minimal error in the optimization dataset then tested in a third, validation dataset (N=10) to ensure that overfitting had not occurred in the training or optimization datasets (Hacker et al., 2013).

The training process allowed the MLP to learn a mapping between rs-fMRI correlation maps (from seeds across the brain) and RSN identity. After training, the MLP was applied comprehensively to the entire brain by generating a correlation map for each voxel (treating each voxel as a seed) and then computing RSN estimates by propagating this map through the MLP. Thus, the MLP was used to generate a seven-dimensional RSN estimate for every voxel. In other words, for each RSN, a whole-brain image was produced with an estimate of the likelihood of membership at each voxel.

In those patients with tumors, lesions were manually segmented from T1 and T2 weighted images. For each tumor patient, a new MLP was trained using a process identical to that described above, with the following changes. First, all correlation maps in the training data that were generated from ROIs that intersected the lesion were omitted. Second, the grey matter mask defining the input layer of the MLP was modified to exclude all lesion voxels. The new MLP was then applied to the individual patient, again operating on voxel-wise correlation maps but now ignoring any voxels within the lesion.

To determine the probability that an electrode covers a portion of a RSN, electrode MRI coregistration was performed as described in the next section. The results of the MLP analysis for gray matter voxels located within 30 mm of the electrode were averaged with a weight that

was inversely proportional to the square of its distance from the electrode. The inverse square law describes the behavior of voltages in the brain that arise from electrical dipoles. This analysis was performed for each of the seven resting state networks, and the results were normalized so that a sum over the probabilities for all networks was equal to one for each electrode.

4.2.3 Electrode MRI Coregistration

The method we have developed allows for the precise alignment of the subdural grid to the surface of the brain, and is similar in concept to the methods used by Hermes et al. (Hermes et al., 2010) and He et al. (He et al., 2008) Preoperative MP-RAGEs were acquired using standard clinical protocols. CT images were acquired prior to removal of the grid. CTs were transformed to atlas space using a cross-modal procedure based on alignment of image gradients(Rowland et al., 2005) in which the CT image is aligned to the individual subject MP-RAGE, and the MP-RAGE is then transformed to an atlas-space(Talairach and Tournoux, 1988) representative target using a 12-parameter affine transformation. Electrodes in the CT image were often found to be in contiguous clusters due to artifact induced by the presence of wires and the extreme intensity of metal electrodes in x-ray based modalities. Electrodes were segmented by a combination of voxel erosion, a 5mm Gaussian blur, and thresholding. Center-of-mass coordinates from clusters of face-contiguous voxels were isolated using an in-house clustering algorithm. A supervised electrode trimming tool (designed in MATLAB) was used to remove remaining metal artifacts (wires, clips, etc) as well as sort the grid electrode coordinates.

Due to rigidity of the grid materials, the locations of the electrodes at the time of CT acquisition are generally displaced inward relative to the location of the subject's cortical surface at the time of MRI acquisition. To correct for this, electrode coordinates were projected to the

surface of the brain along a path normal to the surface of the grid. The surface anatomy used in this procedure was extracted using Freesurfer 5; the segmented pial surface was filled and then blurred modestly (2 mm) such that electrodes arrive at a location reflecting the smoothed convexity of the brain.

4.2.4 Electrocortical Stimulation Mapping

Electrodes were classified as covering eloquent cortex or not with the use of the gold standard of ECS mapping. For the epilepsy patients, ECS mapping was performed independently by a neurologist in the extraoperative setting to localize motor, sensory, and language cortex before subsequent resection of seizure foci. This mapping took place late in the telemetry, after the successful identification of seizure foci and before the second craniotomy. ECS was performed using cortical stimulation with bipolar stimulation of pairs of adjacent electrodes at a frequency of 60 Hz and pulse width of 500 ms. The current was gradually increased from 1 mA to 10 mA or until the afterdischarge threshold was reached. Stimulation duration for motor and language mapping was 3 to 5 seconds. For each stimulated electrode pair, motor regions were defined by the presence or absence of induced involuntary motor movements was noted. Language sites were noted when speech arrest occurred during the stimulation of an electrode pair (see Figure 4.2A). For the tumor patients, the process of ECS mapping was similar to the epilepsy patients, but was performed intraoperatively using a hand held Ojemann stimulator (rather than a grid array of electrodes) prior to tumor resection. Otherwise the stimulation parameters were similar. Only ECS positive sites were noted in the tumor subjects and registered in three dimensional space on an MP-RAGE T1 MRI scan (using Medtronic Stealth Navigation) and subsequently coregistered in the method described above.

A. Resting State fMRI Mapping **RSN** Topography Dorsal Attention Ventral Attention Pre-Op Mapping Somatomotor Visual Implanted Grid Frontoparietal Control Coregistration and Post-Op Analysis Language Default Mode Network B. Stimulation Mapping Functional No response Response High ECS Sensitivity High ECS Sensitivity, Pairwise High ECS Specificity

Figure 4.2. Schematic for classifying electrodes as motor or language positive using resting state fMRI and the gold standard electrocortical stimulation (ECS) in epileptic patients. A) Seven RSN maps were constructed using the multilayer perceptron (MLP) algorithm for each patient. From these seven networks, motor and language maps were investigated further; after coregistering the electrode grid to the MR data, gray matter voxels located within 30 mm of each electrode were averaged with a weight that was inversely proportional to the square of its distance from the electrode. Electrodes greater than a minimum threshold were then classified as motor or language positive for the MLP (red triangles). This threshold was varied to obtain ROC curves. B) ECS was used as the gold standard for identifying motor and language cortex. All electrodes that did not evoke a functional response were classified as ECS negative. For the high ECS sensitivity method of classifying ECS electrodes, any site evoking a motor or language response was classified as ECS positive. This method was also used to employ a pairwise

analysis. For the high specificity method of classifying ECS electrodes, electrodes that were associated with a functional response were classified as ECS positive, provided that they were not also involved in a stimulated pair that did not evoke a response, in which case they were still labeled ECS negative.

For the epilepsy patients, electrodes were classified as motor or language positive using three different methods of classification. In all three methods, any electrodes that did not evoke a motor or language response when stimulated were labeled negative. In the first more sensitive method (Figure 4.2B, high ECS sensitivity), all sites inducing a motor or language response were classified as ECS positive. In the second method (Figure 4.2B, high ECS sensitivity, pairwise), all sites inducing a motor or language response were considered ECS positive as a pair. In the third more specific method (Figure 4.2B, high ECS specificity), electrodes that were associated with a motor response when stimulated were classified as motor positive, provided that they were not also involved in a stimulated pair that did not evoke a response, in which case they were still labeled negative. This method was more restrictive and resulted in fewer electrodes being classified as motor positive. Because there were a limited number of electrodes associated with speech arrest, there were an insufficient number of electrodes to use this method of classification for language sites.

4.2.5 Comparison of fMRI Analysis and ECS Mapping

The result of the MLP analysis for a single electrode was a seven-element vector representing the likelihood that the electrode was a member of each of the seven RSNs. As a method of validation, in this study we focused primarily on the motor and language networks in the epilepsy subjects. For those networks, an electrode was classified as positive or negative from the MLP results if the probability was greater than or less than a specified threshold, respectively. This threshold was varied from zero to one and at each threshold the true positive rate was plotted against the false positive rate, yielding a receiver-operator curve (ROC). Each epilepsy patient was analyzed individually, yielding multiple ROC curves for each analysis. These ROC curves were averaged and the area under the curve (AUC) for this line was used as a measure of the agreement between the MLP method and the gold-standard ECS method.

In the case of the high ECS sensitivity pairwise analysis, the ROC curves varied slightly. The MLP results were considered in pairs of cortical regions related to the ECS electrode pairs overlaying them. An MLP pair was considered positive if either one or both of the pair of cortical regions were positive for motor or language, since this implies that eloquent cortex was present in the area of at least one of the ECS electrodes.

For the comparison of fMRI analysis and ECS mapping in tumor patients, a quantitative analysis was impossible because negative ECS results were not recorded. However, ECS positive sites were recorded in two patients, making a qualitative analysis possible (Figure 8).

4.3 Results

RSN maps were produced for all epileptic patients in the study (Figure 3). For networks in which no direct clinical comparison was possible, the acquired maps were in good agreement with published results. These included the visual network (VIS) (Beckmann et al., 2005, Damoiseaux et al., 2006), dorsal and ventral attention networks (DAN, VAN) (Fox et al., 2006a, Seeley et al., 2007), frontoparietal control network (FPC) (Dosenbach et al., 2007, Vincent et al., 2008, Power et al., 2011), and default mode network (DMN) (Raichle et al., 2001, Greicius et al., 2003). For the motor and language networks, which were compared to the clinical findings using ECS, there was a high degree of qualitative overlap between the two methods (Figure 4). The positive motor ECS electrodes were centered in the pre-central gyrus. The MLP derived motor areas encompassed both the pre- and post-central gyrus. The positive language ECS electrodes were centered in the pars opercularis area of the inferior frontal gyrus (IFG) (approximately Brodmann area (BA) 44) posterior to the MLP language positive regions, which were in the pars triangularis of the IFG (approximately BA 45). Quantitative comparisons were performed with an ROC analysis.



Figure 4.3. RSN maps produced by the multilayer perceptron (MLP) algorithm for the six epilepsy patients in the study.

For each patient, the language (LAN), somatomotor (SMN), visual (VIS), dorsal attention network (DAN), ventral attention network (VAN), frontoparietal control (FPC), and default mode network (DMN) were all mapped. The raw outputs of the MLP are estimates of the probability of class membership. For the purposes of visualization, the values displayed here are percentiles after rank ordering the data for each RSN across the cortex.



Figure 4.4. Visualization of the results for motor and language cortex using both ECS and the mulitlayer perceptron (MLP) in the six epilepsy patients.

ECS results are shown with colored triangles for ECS positive sites and black circles for ECS negative sites, while the MLP color maps are shown on the cortex surface. In the left column, the high ECS sensitivity method was employed to classify motor electrodes as ECS positive (red triangles) and compared to the MLP results (light blue). In the middle column, the high ECS specificity method was employed to classify motor electrodes. In the right column, the high ECS sensitive method was used to classify language electrodes as ECS positive (green triangles), with the MLP results displayed in orange. Patient 3 had no ECS positive language sites and was thus excluded from the analysis.

4.3.1 ROC Analysis

The results of the ROC pairwise analysis can be found in Figure 5. ROC analysis yielded an average AUC of 0.89 for the motor network and an average AUC of 0.76 for the language network. ROC curves for the non-pairwise analysis can be found in the supplemental Figure. Using the method of high ECS sensitivity, an average AUC of 0.80 for motor and 0.64 for language were found. When using the method of high ECS specificity, only motor had a sufficient number of electrodes to perform an ROC analysis, and the AUC was found to be 0.82.



Figure 4.5. ROC curves for epilepsy patients comparing motor and language electrode identification by the multilayer perceptron (MLP) algorithm to the gold standard ECS. In this pairwise analysis, an MLP pair was considered positive if either one or both of the pair of cortical regions were positive for motor or language, since this implies that eloquent cortex was present in the area of at least one of the ECS electrodes. The gray lines represent ROC curves for the individual patients and the black line is an average over the patients. The area under the curve (AUC) listed is for the average over the patients. The brains shown are the anatomic representations of these networks for a given threshold. Namely, a higher threshold (the lower brain) has elevated specificity and lower sensitivity and a lower threshold (the upper brain) has lower specificity and and higher sensitivity.

4.3.2 Minimization of False Negatives

When evaluating the performance of pre-operative rs-fMRI with ECS mapping, the goal was to minimize false negatives, in which electrodes are incorrectly classified as non-eloquent cortex by the MLP when they are eloquent cortex as determined by ECS, to reduce motor or language surgical morbidity. To minimize the number of false negatives, a procedure was designed in which a threshold for motor classification was determined, and then a "no-cut" area was expanded around those electrodes to determine how far one must move beyond the MLP classification of motor to minimize false negatives. The results of this analysis can be seen in Figure 4.6 for several thresholds. A visualization of this procedure, performed at a threshold of 85% and a distance of 15mm (marked by the arrow in Figure 4.6A), is shown in Figure 6B. For multiple thresholds, at a 15 mm distance from the edge of the motor network there were only 4 electrodes across the six patients that were false negative. Thus, when taken across all electrodes and all patients the risk probability for missing a stimulation positive site is less than 2% across all thresholds.





A) To define the area, several multilayer perceptron (MLP) thresholds (70, 75, 80, 85^{th} percentiles) were used to classify electrodes as covering motor cortex, and the "no-cut" zone was expanded around each of the motor electrodes. The probability of a missed motor electrode, which could result in motor deficits, was plotted against the radius of expansion. **B**) A visualization of the method performed at the 85% and at a radius of expansion of 15 mm. Red triangles mark motor cortex as determined by ECS that were missed by the MLP method.

4.3.3 Results in Tumor Patients

The results of the MLP analysis of tumor subjects can be seen in Figures 4.7 and 4.8. Figure 4.7 reveals network distortion in the presence of tumors. The structural images in the left column reveal the extent of the lesion in each patient. Columns 2, 3, and 4 contain axial, coronal, and sagittal views, respectively, of the MLP results displayed in a winner-take-all format. Significant anisotropy across the midline can be seen in the networks present in areas near the tumor, which is consistent with previously published findings (Zhang et al., 2009). Networks were preserved in the presence of a tumor, though they were often shifted from their normal anatomic position. In three of the six patients (1T, 3T, and 7T), the motor network was shifted posteriorly in the tumor hemisphere relative to the unaffected hemisphere. This effect was particularly pronounced in patient 1T, where in the sagittal view, one can see that the section of motor strip superior to the tumor remains in its normal anatomic location, but the inferior portion was shifted posteriorly to the edge of the tumor. An extension of this effect can be seen in the language area of patient 7T, where the language network was shifted posteriorly in the tumor hemisphere. Additionally, networks distant to the tumor also appeared perturbed. In patient 7T, it appears that the visual network has contracted in the tumor hemisphere relative to the non-tumor hemisphere despite the tumor being located in the frontoparietal network, where one might assume it would have no effect on the visual network. This effect can also be seen to a lesser extent in patients 1T and 3T, with the visual network covering a larger area in the unaffected hemisphere than the tumor hemisphere.



Figure 4.7. RSN maps produced by the multilayer perceptron (MLP) algorithm for six tumor patients in the study.

The language (LAN), somatomotor (SMN), visual (VIS), dorsal attention network (DAN), ventral attention network (VAN), frontoparietal control (FPC), and default mode network (DMN) were mapped in a winner-take-all format in the area of the tumor. For the purposes of visualization, the values displayed here are percentiles after rank ordering the data for each RSN across the cortex and subsequently smoothed using a Gaussian filter with a standard deviation of 6mm.

Despite the level of distortion, for those two patient where stimulation was performed (Figure 8) there is still agreement between the gold-standard of ECS, marked by black dots, and the perceptron results, shown as color maps on the cortex surface.



Figure 4.8. Visualization of the results for identifying eloquent cortex using both ECS and the mulitlayer perceptron (MLP) in two tumor patients.

ECS results are shown with black circles identifying positive motor and speech sites. The MLP color maps are shown on the cortex surface, with blue representing the somatomotor network (SMN) and orange representing the language network (LAN). Patient 2T had no motor positive sites identified by ECS so the MLP-identified SMN network is not shown.

4.4 Discussion

While task-related fMRI has shown great promise as a pre-operative brain-mapping tool for neurosurgical planning (Adcock et al., 2003, Haberg et al., 2004, Vlieger et al., 2004, Matthews et al., 2006), the requirement that patients be awake, alert, and cooperative limits its use to a wider patient population (Pujol et al., 1998). More recently the use of the brain's taskindependent endogenous activity has been proposed as a new method to identify eloquent regions in the brain (Zhang et al., 2009). Correlated fluctuations in resting state metabolic activity, as measured with BOLD fMRI, has been well established as a metric for identifying functionally connected networks (Fox and Raichle, 2007). Previous studies have demonstrated that the cortical topographies associated with a given resting state network closely correlate with the cortical regions associated with a task-based activation (Smith et al., 2009). The feasibility of this approach has been preliminarily investigated in the setting of preoperative brain mapping (Kokkonen et al., 2009, Liu et al., 2009, Zhang et al., 2009). Despite the substantial scientific and more limited translational efforts performed thus far, there is still a substantial need for technical expertise to visualize these networks and therefore limited to more specialized centers. The purpose of this study was to investigate the possibility of using a data driven approach that can rapidly, effectively, and independently identify cortical networks. To achieve this goal, we selected a subset of the identified networks traditionally thought to be eloquent in nature and compared them with the clinical gold standard of electrocortical stimulation (ECS). To further define the clinical utility of this approach, we investigated the localization of eloquent cortex in patients with distorted anatomies due to mass lesions. Here we show that through the use of a novel artificial neural network approach, known as the MLP, that seven canonical networks can be identified with a single 30 minute scan. Moreover, there is strong concordance between language and somatomotor resting state networks with ECS localization. Taken together, these findings provide evidence that resting state fMRI and neural network classification of imaging data can potentially provide a novel tool for neurosurgical brain mapping in the future.

Two predominate strategies that have been used to map RSNs with rs-fMRI are seedbased correlation mapping (see Introduction and Zhang et al (Zhang et al., 2009)), and independent component analysis (ICA) (Beckmann et al., 2005). ICA is often thought of as advantageous because it performs a blind separation requiring no priors and is thus an unsupervised method. However, if ICA is used to localize RSNs, a post-hoc assignment must be performed to identify the 'correct' component from an arbitrarily ordered set. This is usually performed by expert viewers or by evaluating similarity with a pre-defined template (Tie et al., 2013). In addition to the burden of identifying components, there is no guarantee that components recovered in different subjects and identified as a particular RSN (e.g., "language") actually represent the same entity. The MLP is a supervised method trained to identify known RSNs. The outputs of this method always represent the same entity, ordered in the same way. For this reason, the trained MLP represents a fully automated solution to estimating RSNs in individual subjects and is well suited for clinical implementation (Hacker et al., 2013).

A cornerstone of this study was the comparison of resting state functional MRI to cortical stimulation. The differences in the information acquired from these two modalities, however, deserve mention since they impact the interpretation of the results. While the ROC curves demonstrated good agreement between the MLP and the gold standard of cortical stimulation (particularly in identifying motor cortex), there were also regions that did not overlap. This was in part due to the differences of what each of these modalities detect. ECS identifies only those parts of the cortex "essential" for function; the MLP identifies these regions in addition to regions that may produce deficits detectable only by detailed neurocognitive testing, or not at all. In the case of motor localization, the MLP identifies the somatomotor network which encompasses both primary motor and primary sensory cortex. ECS, on the other hand, only identifies primary motor cortex by eliciting a motor response. Consistent with this difference, the ECS positive sites were localized to the pre-central gyrus, whereas the MLP- defined motor network included the pre-central and post-central gyri and some insular cortices. The discrepancy in extent of cortex identified with each method was more pronounced with language, where the MLP-defined language network extended broadly beyond cortical areas associated with stimulation responses. The difference between the language ECS positive sites and the MLP-defined language areas occur because ECS identifies regions that produce speech arrest, whereas the MLP identifies other regions related to the higher cognitive aspects of language. This demonstrated a dissociation between regions related to vocalization (primarily BA 44, REF) vs. cognition. This dissociation has two major implications for pre-surgical planning: 1) Machine learning techniques such as the MLP could be specifically trained to localize regions associated with speech (as opposed to language, broadly defined). 2) Inversely, deficits detectable by post-surgical neurocognitive testing could be related to damage to other MLP-defined regions of higher cognitive function. Information of this type could be used to study the relationship between surgical lesions and cognitive deficits related to the various RSNs, and ultimately, could be used by neurosurgeons to prevent increasingly wider ranges of cognitive deficits. Despite these differences, an important consideration from a surgical planning standpoint is the false negative rate of a region identified with the MLP. This is the more clinically significant error, namely, when a site is misidentified as being non-functional when it actually is eloquent. In the case of motor cortex (due to having sufficient data) we show that MLP performs reasonably well. The likelihood that an electrode was misidentified as nonfunctional drops substantially between 1-2 cm from the border of the functional zone.

To date, functional MRI has facilitated a "preoperative anatomic awareness" of an eloquent region's association to a given lesion or site of neurosurgical interest. In essence, this

information gives the neurosurgeon helpful, but non-definitive, information that can aid his or her surgical strategy (e.g., regions to avoid, areas that will require intraoperative cortical mapping, etc). The most common types of eloquent cortex are regions subserving motor and language function. Localizing these areas, however, requires that the patient be conscious, attentive, and capable of participating in the given cognitive paradigm. In the setting of a brain tumor, effective participation may be impaired due to a neurologic deficit or confusion. Additionally, because the patient must be awake during the imaging procedure, sedation cannot be used, thus eliminating pediatric or claustrophobic patients. Because resting state networks are task independent and have been shown to be present despite the level of consciousness (i.e. sleep or anesthesia), the limitations of task-based functional MRI do not apply and thus makes this approach substantially more widely applicable. In this study, we have demonstrated that in regard to motor and language function there is close correspondence between the anatomic locations of motor and language findings identified with the neurosurgical gold standard of cortical stimulation. While this in no way negates the need for stimulation, it does provide external validation that this automated method identifies useful functionally relevant information that can potentially enhance a surgeon's anatomic awareness of motor and language cortex prior to a surgery.

Having demonstrated a correspondence between the resting state language and motor networks in patients with normal anatomy, the next phase of the study was to investigate these networks in patients with distorted anatomy. The qualitative correspondence between ECS mapping and MLP results in two tumor patients suggests that despite physical perturbation, the MLP was still able to correctly identify networks adjacent to the tumor. In addition to the demonstrated utility of this method for functional localization, these findings also support the durable nature of resting state networks that persist in the presence of physically disruptive lesions. Also of note, there were areas within the tumor that also demonstrated network connectivity. These findings would be in alignment with previously published findings by Skirboll et al. that found stimulation positive sites for motor and speech within the substance of the tumor (Skirboll et al., 1996). Beyond perilesional distortions, there were also notable qualitative differences in networks distal to the lesion. Most notably, visual cortex had a reduced anatomic representation ipsilateral to the tumor. These findings could suggest that local dysfunction can have distant effects on networks not directly involved by the tumor. Alternatively, there were also some cortical network assignments for visual cortex that were found in frontal lobe that could also suggest the MLP incorrectly assigned network locations.

In addition to broadening the patient population that can be preoperatively mapped, the use of the MLP for the identification of multiple cortical networks also broadens the capability of what cognitive operations can be assessed, and can potentially redefine what regions are considered "eloquent." The correlation between stimulation mapping and the somatomotor and language resting state networks supports that the other cortical networks identified are also functionally relevant. It is important to note that motor and language are the cognitive operations that are typically screened for both preoperatively and intraoperatively. Other cognitive operations of attention, executive control, and sensory perception are challenging if not impossible to screen for pre- and intraoperatively in a comprehensive fashion. Either the number of tasks needed to identify all these functionally relevant regions would simply be too long to test in an MRI, or there are no ways of eliciting or interrupting these complex cognitive operations in

the operating room in a reliable way. While it is critical that a surgeon preserve a patient's ability to move and speak after surgery, these other cognitive operations and their associated networks may also play a role in long-term clinical outcomes which are harder to test. The use of automated methods to rapidly classify all these networks with a single brief scan may provide an important tool to enable a more subtle appreciation for how these patients will cognitively perform clinically beyond simple motoric and linguistic tasks. As an example, identification of the dorsal attention network may better inform a parietal approach to mitigate a postoperative neglect (Corbetta and Shulman, 2002). Similarly, a surgery affecting the fronto-parietal control network may impact a high functioning professional's decision making process (Dosenbach et al., 2007, Vincent et al., 2008). While the impact of surgery on these various networks needs to be explicitly tested before any clinical recommendations can be made, this approach can at least provide the tool to address such questions.

There were several limitations to the present study. The first limitation was the small number of patients, which permitted meaningful but still preliminary results. More definitive results which will aid in guiding clinical management will require acquiring a higher number of subjects. Second, both the electrode grid coverage and spatial resolution were limited, however this is typical for the data obtained from current electrocortical grids. Third, this study looked at speech arrest for the identification of language areas using ECS, but for language cortex identification paraphasic errors also is an important functional measure (Duffau et al., 2003, Gatignol et al., 2004) which was not included in the study. Fourth, in the context of tumors, there were some unusual findings in the visual cortical network assignments that could suggest that MLPs may have reduced accuracy when regions are anatomically distorted. Fifth, the study

lacked clinical outcomes. Finally, while the group average numbers were encouraging, results for individual patients may not be satisfactory. In particular, despite a low false negative rate in Fig. 6B, two of the four false negatives were found in patient 3, which could result in surgical morbidity if not correctly identified. Taken together, these results are exciting, but will require a larger clinical series to assess their impact on clinical practice.

In summary, the mapping of resting state networks defined by rs-fMRI offers a new method for preoperative planning, and the use of the novel artificial neural network presented here can automate and speed the presurgical processing of rs-fMRI data. These techniques not only localize motor and language regions classically understood to be eloquent, but also enables the identification of all the canonical functional networks. Taken together, because this approach is task independent and can identify a multitude of networks simultaneously, these findings stand to enhance preoperative imaging by substantially expanding the patients that can be mapped and better interrogating all regions of function in the human brain.

4.5 References

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Supplemental Figure. ROC curves comparing motor and language electrode identification by the multilayer perceptron algorithm to the gold standard ECS. The gray lines represent ROC curves for the individual patients and the black line is an average over the patients. The area under the curve (AUC) listed is for the average over the patients. The top row displays the results of the ROC analysis for the method of high ECS sensitivity classification for motor (Figure 4, column 1) and language (Figure 4, column 3). The bottom row contains the results of the ROC analysis for the method of high ECS sensitivity classification for motor (Figure 4, column 2).

Age (y)	Seizure	Seizure	Duration of	Antieptileptic	ECS-positive	Handedness	Wada
	Туре	Foci	epilepsy (y)	Medications	Language Sites		Testing
49	СР	ATL	48	LMT, TPM	Yes	Right	Bilateral
36	СР	ATL	35	VPA, TPM	Yes	Left	Bilateral
52	СР	PFL	51	CLZ, VPA, LRZ, OCB	No	Right	Not Done
28	СР	PFL	14	CBZ, CLZ, LMT, LRZ	Yes	Right	Not Done
49	СР	ATL	4	LRZ	Yes	Right	Not Done
34	СР	ATL	20	LMT, LEV, ZNS	Yes	Right	Not Done

Table 4.1: Demographic and clinical information for seizure patients.

ATL, anterior temporal lobe; CBZ, carbamazepine; CLZ, clonazepam; CP, complex partial; LEV, levetiracetam; LMT, lamotrigine; LRZ, lorazepam; OCB, oxcarbazepine; PFL, posterior frontal lobe; TPM, topiramate; VPA, depakote; ZNS, zonisamide.

Age (y)	Tumor	Pathology	Handedness
	Hemisphere		
32	Left Frontoparietal	Low Grade	Right
		Astrocytoma	
48	Left Temporal	Astrocytoma	Right
37	Left Frontal	Low Grade	Right
		Astrocytoma	
43	Left Frontoparietal	Low Grade	Right
		Astrocytoma	
36	Left Frontal	No surgery/pathology	Right

57	Left Parietal	Astrocytoma	Right
41	Left Frontotemporal	GBM	Right

Table 4.2: Demographic and clinical information for tumor patients.

No Wada testing was performed on any of the patients. GBM: Glioblastoma Multiforme

Chapter 5: ECoG Local Field Potential and Band-Limited Power Correlations of Resting State fMRI

The following project was conceived by Eric C. Leuthardt, Maurizio Corbetta, Abraham Z. Snyder (AZS), and Carl D. Hacker (CDH). CDH performed all analyses and writing. AZS assisted in data preprocessing and coregistration for ECoG subjects.

5.1 Introduction

Functional connectivity as assessed by resting-state fMRI (rs-fcMRI) is increasingly used to study the brain's functional organization, yet the electrophysiologic underpinnings of these phenomena remain uncertain. Recent invasive electrophysiological studies in humans have suggested that fluctuations in slow cortical (SCP, < 0.5 Hz) and delta potentials, as well as slow fluctuations in gamma (70-110 Hz) band-limited power (BLP) envelopes are the strongest correlates of spontaneous BOLD (He et al., 2008, Keller et al., 2013). In this study, we systematically investigated the degree to which other frequencies exhibit correlations corresponding to BOLD. We sought to determine a) whether there is regional specificity in the LFP:BOLD relationship, b) whether there exists spectral focality vs. scale-free structure in ECoG:fMRI spatial correlations and c) the difference between the correlation structure of the LFP carrier vs. its BLP envelope.

The first goal of this study is to expand the current understanding of slow LFP phase synchrony as a correlate of BOLD functional connectivity across frequencies and networks. Phase synchrony in low frequencies has been proposed as a mechanism that coordinates the excitability of neuronal assemblies throughout the brain (Fries, 2005). Given that slow cortical potentials (SCP, rhythms < 0.5Hz) show correlations that reflect functional organization of motor cortex at rest (He et al., 2008, Breshears et al., 2010), we hypothesize that significant SCP correlation within BOLDdefined networks will generalize to other RSNs. The second goal of this study is to determine whether specific frequencies exhibit spatial ECoG:fMRI correspondence. Given the important of low frequency oscillations (in the theta, alpha, and beta ranges, or 4 to 20 Hz collectively) in functional systems (Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999), we hypothesize, in contrast to (He et al., 2008), that LFP correlation topographies significantly corresponding to RSNs will extend beyond delta (1-4 Hz) oscillations. Finally, we will compare the frequencies of ECoG:fMRI spatial correspondence found with LFPs to that of the BLP envelopes. He et al., 2008, and Keller et al., 2013, have shown spatial correspondence between fMRI correlations and correlations of band-limited power fluctuations of gamma frequencies; in this study we investigate the degree of ECoG:fMRI correspondence for lower BLP carrier frequencies and compare the spectral structure of ECoG:fMRI correspondence for BLP and LFP correlations.

5.2 Methods

5.2.1 Image Acuisition and RSN Definition

Structural and functional imaging acquisition followed standard methodology (Hacker et al., 2012). We acquired at least 30 minutes of resting state data in each participant. Because these participants are rare and valuable, we sought to minimize the possibility of excluding participants due to insufficient BOLD data after rigorously quality control procedures (Power et al., 2012). Initial fMRI preprocessing followed conventional practices (Shulman et al., 2010). Briefly, affine volume registration was performed with retrospective EPI distortion correction using the

FUGUE module in FSL (Jenkinson et al., 2012). Field maps were approximated using the technique described by Gholipour and colleagues (Gholipour et al., 2008). Nuisance regressors included white matter, head motion, CSF, and the global signal (GSR) averaged within a brain mask. Individual frames were censored using a threshold of 0.4% RMS Δ frame intensity (dVar), resulting in an overall average of 3.8% of steady-state frames removed.

Traditionally, RSNs have been defined by ICA (Damoiseaux et al., 2006) or seed-based analyses (Fox et al., 2005). We have developed a robust technique (Hacker et al., 2013) that computes continuous estimates of membership in each network for every locus in the brain; thus any location can partially belong to multiple networks or to none. Briefly, our method relies on first computing a seed-based fMRI correlation map for each brain locus. The algorithm uses this correlation map to estimate the scalar [0,1] membership in each RSN. The core of this technique is a neural network (specifically, a multi-layer perceptron performing non-linear regression) that has been trained to associate correlation maps of a standard set of task-derived seed regions with predefined RSN labels. Importantly, RSN estimation performance with standard seeds was comparable between ECoG participants and age-matched control subjects. After registration, fMRI timeseries and perceptron-defined RSN maps were sampled to electrodes by modeling grey matter as a superposition of diploes in 3-D space (see Chapter 2 for details on ECoG:fMRI registration). Thus, this method produced, for each electrode, one membership estimate per RSN defined in Hacker et al., 2013 (Dorsal Attention, Ventral Attention, Motor, Visual, Frontoparietal Control, Default Mode).

5.2.2 Subjects and Coverage

Participants were patients at Barnes Jewish Hospital with refractory epilepsy undergoing

ECoG monitoring to localize seizure foci. Data were analyzed from 11 participants for this study.

Implanted electrodes (platinum, 4 mm, 2.3 mm exposed, PMT corporation) were 8x8 or 6x8 grids (with 1 cm spacing) and strips (1x4, 1x6, or 1x8), placed subdurally facing the cortical surface. A separate strip facing the skull serves as ground and reference for the amplifier (Proamp, Lamont Medical Inc). ECoG data were recorded on these clinical amplifiers at 512 Hz. The multi-day records were to produce an average of 14 hours of data across 20 runs per subject.

Acceptable RSN coverage was defined as at least 15 electrode pairs (separated by >20 mm) where both electrodes achieve classifier scores above the 70th percentile of all brain voxels. RSN coverage in each subject, as well as the number electrodes and amount of ECoG data acquired, are summarized in Figure 5.1.

RSN Coverage											
	1	X		Х	Х	Х	Х		19	6.4	100
) de	2	X		Х		Х	Х	X	14	5	116
	3	X		Х	х	Х	х		11	5.7	102
L	4	X		х		Х	х		14	6.5	84
ן א	5	X		х			х		16	19	48
al	6	Х	х	х		Х	х	X	22	5.2	94
ip	7	Х			х	Х	х	Х	18	9	102
<u>.</u>	8			Х			х		15	15	72
art	9	X	Х	х	x	Х	х	X	24	14	88
ñ	10	X	х	х		Х	Х	X	12	14	88
	11	X		х			Х		11	4.5	84

Figure 5.1. ECoG Data and RSN Coverage

Available data in 11 subjects. RSN coverage is defined by at least 15 electrode pairs (of at least 20mm separation) in a given network. Runs indicates the number of segmented epochs of ECoG data analyzed for spontaneous correlations.

5.2.3 ECoG Processing

ECoG Data were screened for artifact by inspection of time-series data, power spectra, and time-frequency plots for channels with excessive noise and epochs with excessive environmental noise across all channels. Channels exhibiting inter-ictal activity were also excluded (0.7 per participant avg.). Included signals will be referenced to a common average. A de-spiking function, $f(x) = A * \operatorname{atan} (x/A)$, where *A* is 3 s.d. of the signal, is applied to attenuate artifacts from nearby medical devices (e.g., IV pumps).

After re-referencing signals to a common average, we decomposed signals using zerophase digital filtering using a 2nd order Butterworth filter in the forward and reverse directions (effectively, 4th order). 25 logarithmically spaced frequency bins were defined between 2 and 150 Hz for BLP analyses. Filtered signals were squared to produce instantaneous power, then further band-pass filtered to isolate specific envelope frequency components. For LFP analyses, frequencies extending down to 0.5 Hz were considered for SCP analyses. The spectrum of an envelope signal has an upper frequency limit of half the bandwidth of the carrier band. We lowpass filter all BLP signals to ensure similar spectra. The strongest inter-hemispheric correlations in MEG can be found after filtering for the lowest frequencies of BLP envelopes (<0.1 Hz) (Liu et al., 2010). This result and the intention to match the frequencies of BLP envelopes.

5.2.4 Correlation vs. Distance Trend Removal

Correlation maps were computed as the Pearson product-moment correlation across all pairs of electrode timeseries, treating the fMRI and ECoG BLP timeseries identically. Correlations of both ECoG and BOLD signals are systematically greater at shorter distances.
Locally increased correlations may be induced by spatial smoothing of BOLD data or volume conduction of deep source in ECoG data. However, distant dependent correlations are expected to be largely driven by true physiologic correlation. Such systematic correlation:distance relationships increase the apparent similarity of ECoG and BOLD correlation maps and therefore decrease the sensitivity of ECoG:fMRI spatial correlations to topographically specific features. The inverse relation of correlation to distance can artifactually introduce long-distance correlations if the distance dependence is removed by linear regression. Thus linear distance regression can generate spurious similarity between ECoG and BOLD correlation maps. Therefore, to maximize sensitivity to RSN topography, the correlation:distance relationship was removed using B-spline regression (see Figs. 5.2 and 5.3).



Figure 5.2. Pair-wise temporal fMRI correlations across ECoG electrodes.

A. Estimate of RSN identity of each surface locus in an individual based on supervised classification of seed-based BOLD correlation maps. B. Exemplar BOLD timeseries after sampling surface-processed timeseries to electrodes using the weighting function described in Extended Data Fig. 2. C. Temporal correlation matrix of BOLD signal between all pairs of electrodes after spline regression of distance-related correlation trends (see Extended Data Fig. 4C).



Figure 5.3. Pair-wise Temporal ECoG Correlations

A. 10 Hz signals filtered from two exemplar channels. Thin lines indicate the filtered LFP (carrier wave). Thick lines indicate the band-limited power envelope. B. Euclidean distance across all pairs of electrodes. C. Relationship of correlation values to electrode distance in raw data with a two parameter fit. D. Pairwise temporal correlation between electrodes corresponding to the data in C. E&F. Correlations after re-referencing data to a common average.

5.2.5 ECoG:fMRI Comparison Methodology

We used two general strategies to determine ECoG:BOLD topographic correspondence: 1)

a conceptually simple method contrasting within- vs. across-RSN electrode pairs; 2) a method comparing topographies parametric in ECoG frequency and electrode location.

Within-RSN vs. Across RSNs: Given a thresholded BOLD RSN map, each electrode is either within or outside an RSN. We contrasted correlations of electrode pairs: both in vs. one in and one out (Fig 1A). This contrast is inherently biased by electrode distance effects (within RSN pairs are generally closer). Previous studies have partially corrected this bias using linear regression (He et al., 2008), but correlation as a function of inter-electrode distance clearly is not linear (Fig 1B). To remove systematic distance effects, we model and subtract this effect from the data using locally weighted scatter plot smoothing (LOWESS) (Cleveland, 1979) on the ensemble of all pairs at each frequency. This method is conceptually simple and delivers clearly interpretable results. However, the necessity of thresholding means that some information is lost. Beyond this, this method uses sparse sampling of the data, only considering a subset of correlations.

Spatial Correspondence: To consider the data in a more complete fashion, we used a spatial covariance-based approach. This method directly compared the topography of ECoG and fMRI correlation maps and. The ECoG correlation map was first computed at a given locus and frequency; its spatial covariance with fMRI correlation maps produced at the same location was then computed. This produced an estimate of correspondence at each frequency for every electrode. This method is sensitive to graded topographies and avoids modeling RSNs as discrete patches with hard boundaries.

This method was performed parametric in carrier frequency for correlations of bandlimited signal (carrier) correlations (LFP) and band-limited power (envelop) correlations (BLP).

5.3 Results

5.3.1 Within- versus Across-RSN Comparison

A within-RSN vs. across-RSNs comparison of correlations is illustrated in Figure 5.2 for the sensorimotor (SMN or Motor) RSN for an individual subject. After distance regression (see 5.2.4), within-sensorimotor network pairs (red) had systematically greater correlations than crossnetwork pairs (blue). Notably, these RSN-specific ECoG correlations appear distributed across all ranges of inter-electrode distances, rather than as a local phenomenon. A t-statistic was generated to indicate generally the specificity of ECoG correlations within the SMN (in one temporal epoch for this subject).



Figure 5.4 Exemplar: Within- versus Across-RSN ECoG Correlations.

Left: Brain surface indicating motor RSN topography. **Middle:** SCP correlations between electrode pairs within the motor network (red) vs. across networks (blue) as a function of distance. **Right:** Statistical differences in within vs. across network correlations were summarized using a t-test after removing systematic distance effects.

Within-versus-across RSN analyses were computed for each network in each subject; the

results are summarized in Figure 5.3. Each colored boxplot indicates the variability of computed

t-statistics across temporal epochs for a given subject and RSN. BOLD RSN topographies

corresponded broadly to ECoG SCP correlations in all subjects; significant LFP

correlation:BOLD RSN correspondence was found in multiple networks in every subject.

Correspondence was strongest for motor and visual networks, and weak weakest for the default mode network.



Figure 5.5. Within- versus Across-RSN Comparison: Groups Results

t-statistics are computed for each subject and network as described in Figure 5.4. The variability across runs of each comparison is summarized by a box plot (colored by RSN). Results are aggregated across subjects for each RSN in white box plots.

The summary statistics (white bars in Fig 5.5) are an approximation. Combining t-statistics across runs and across participants is not strictly valid due to differences in distribution and degrees of freedom. A more rigorous approach could involve conversion to Z-scores (Stouffer's method) or log(p) values (Fisher's method). These maneuvers are frustrated by our lack of knowledge of the exact degrees of freedom because the number of independent electrode pairs is an over-estimate of the number of independent correlations within a set of mixed signals (in which the degrees of freedom or number of independent signals is also not known). However, because the number of pairs is generally quite large and yields an approximately normal distribution of correlations after distance regression, the t-statistics approach standard scores and thus can yield a reasonable estimate of the mean and variance of the effect size at the group level.

5.3.2 Spatial Correspondence of ECoG and fMRI Correlations

In the second comparison method, fMRI correlation maps were directly compared to ECoG correlation maps produced from the same region but across multiple frequencies. An example from an individual with a primary motor cortex seed is illustrated in Figure 5.4. Local field potential correlation maps exhibited maximal correspondence with rfMRI at lower temporal frequencies. However, the topography of LFP correlation maps was similar across frequencies, but exhibited linearly decreasing magnitudes across frequency; these trends are reflected by a relatively flat ECoG:rfMRI spatial correlation spectrum, and decreasing spatial covariance. Above beta frequencies the spatial correlation decreased precipitously.



Figure 5.6. Spatial correspondence of fMRI and ECoG LFP correlation maps. A. fMRI signal correlations (computed in the space of electrodes) with a sensorimotor network seed region. **B.** ECoG LFP correlation maps computed with the same seed region at multiple frequencies. **C.** Correspondence spectrum assessed by LFP:fMRI spatial correlation and spatial covariance for electrode location in **A** and **B**. Colored circles correspond to LFP frequencies of exemplars in **B**.

BLP correlations exhibited more interesting phenomenology. The most robust

ECoG:rfMRI correspondence was found within a broad alpha range (6-14 Hz) followed by the

gamma range (70-100 Hz). However, low-gamma range BLP (30-50 Hz) correlations

corresponded poorly to rfMRI and constituted a prominent local minimum in the ECoG:rfMRI

correspondence spectrum. Notably, these analyses involved further filtering of BLP envelopes into separate multiple frequencies (for each underlying carrier frequency). Maximal correspondence with envelope frequency was found in the range of 0.1-1 Hz for both alpha and gamma carrier frequencies.



Figure 5.7. Spatial correspondence of fMRI and ECoG BLP correlation maps. A. fMRI signal correlations (computed in the space of electrodes) with a parietal seed region. **B.** ECoG LFP correlation maps computed with the same seed region at multiple frequencies. **C.** Correspondence spectrum assessed by ECoG:fMRI spatial correlation and spatial covariance for electrode location in **A** and **B**. Note that BLP signals have a carrier frequency (vertical axis) but after rectification can be further filtered into various envelope frequencies for each carrier (horizontal axis). Colored circles correspond to BLP carrier and envelope frequency pairs for exemplars in **B.**

Analyses performed in figures 5.6 and 5.7 were repeated for all electrodes and all subjects, and are summarized in Figure 5.8. At the group level LFP:fMRI spatial covariance decreased linearly with frequency, but LFP:fMRI spatial correlation was roughly constant. In combination, these results indicate that the spatial topographies of LFP correlations are similar across frequencies, but the magnitudes of these topographies decrease. The loss of correlation magnitude with constant topography is evident in the examples in Figure 5.6B and its effect can be seen in the group average spatial covariance curve of Figure 5.8 (red curve, left). BLP:fMRI correspondence exhibited a more complicated relationship with respect to carrier frequency.

Specifically, strong BLP fMRI correspondence was found in theta through low beta frequencies and at high gamma frequencies, but not at low gamma frequencies. And in contrast to LFP correlation maps, BLP correlation maps had magnitudes at high frequencies that were comparable to low frequencies; this is evident in individual examples (Fig 5.7B) and its effect can be seen in the group average spatial covariance curve of Figure 5.8 (blue curve, left).





LFP:fMRI (red) and BLP:fMRI (blue) correspondence spectra are shown after averaging across all electrodes for all subjects computed using spatial covariance (left) and spatial correlation (right). BLP spectra were computed using envelope frequencies over the 0.1 Hz to 1 Hz range for each carrier frequency. Shaded intervals indicate 1 s.e.m. over subjects.

LFP correlation maps exhibited correspondence to rfMRI at low frequencies, while BLP correlation maps exhibited correspondence at both low and high frequenices. To directly assess the similarity these low and high frequency topographies, inter-frequency LFP:LFP and BLP:BLP spatial correlation matrices were computed over all electrode pairs and averaged over subjects and averaged (Fig 5.8). Figure 5.9A reiterates that LFP correlation maps were spatially similar across frequencies up to the low beta range. Notably, there is an absence of cross frequency spatial similarity between low and high frequency LFP correlation maps. At high frequencies, LFP correlation maps were likely dominated by non-physiologic sources of

correlated noise. In contrast, BLP correlation maps exhibited spatial similarity between low and high carrier frequencies (asterisk in Figure 5.9B, cf. red circle in Fig 5.7C). Also note a lack of inter-frequency spatial similarity for BLP correlation maps in the low gamma range (arrow in Fig 5.9B). This feature corresponds to the local minimum of BLP:rfMRI correspondence indicated in Fig 5.7 B&C.



Figure 5.9. Interfrequency spatial similarity of ECoG correlation maps. Matrices indicate the spatial correlation of correlation maps produced from LFPs (**A**) or their BLP envelopes (**B**). Matrices were averaged over all electrodes from all runs across all subjects.

In order to better understand why correlation maps in some frequency ranges show strong ECoG:fMRI correspondence or high interfrequency spatial similarity (e.g. alpha and gamma frequency ranges) when others (e.g., 25-50 Hz range) showed poor ECoG:BOLD correspondence and low interfrequency correlations we estimated the dimensionality of correlation matrices at each frequency as a measure of complexity (Figure 5.10). The dimensionality estimate was based on the maximum likelihood estimation of the number of components using Levina's algorithm. Lower ECoG correlation structure complexity (i.e. smaller intrinsic dimensionality, that is to say fewer components to represent the ECoG covariance) was significantly correlated with higher BOLD correspondence. This was most evident for the local extrema at alpha ("a" in Figure 5.10) and gamma frequencies ("c" in Figure 5.10), as opposed to the lack of correspondence and high dimensionality in the low gamma frequency range ("b" in Figure 5.10).



Figure 5.10. ECoG:BOLD Corresopndence and Intrinsic ECoG Dimensionality A. Mean correspondence spectra for LFP and BLP in one subject. Error bars indicate 95% confidence interval on the mean (14 runs averaging 1 hour each). B. Dimensionality (complexity) of ECoG correlation matrices at each frequency as computed by maximum likelihood estimation. C: Comparison of dimensionality vs. BOLD correspondence across frequencies. Open circles indicate noise frequencies (60 Hz, 120 Hz, above 150 Hz.

5.4 Discussion

5.4.1 Slow Cortical Potential Correlations Within Resting State Networks

He looked at SCPs and gamma in the motor system, but other RSNs were not specifically evaluated. In our restults, spontaneously electrophysiologic correlates of resting state networks were found to be a general property of the brain, rather than a property specific to particular networks or regions.

our results show ECOG fmri correpsomndence only occur for local correlations or long distances equally

Note the equal separation of within vs across correlations as a function of distance in fig 2.

this extends the results of leopold 2003 which had a maximum distance of 1 cm This question requires further study in the subjects that have wide coverage or electrode strips. specifically multiple large grids spaced widely apart. A modest ECoG:BOLD correspondence for the DMN is unexpected given its large contribution to the overall BOLD correlation structure.

5.4.2 ECoG:fMRI Correspondence Across LFP and BLP Frequencies

Correspondence between ECoG and BOLD correlations was found throughout the frequency spectrum, outside of the ranges previously described (infra-slow field potentials and high-gamma power envelopes) (He et al., 2008, Keller et al., 2013). Specifically, previous investigations suggest ECoG:fMRI corresopndence does not extend beyond the delta range for LFPs (He et al., 2008). In our results, LFP:BOLD correlations decreased nearly monotonically with frequency and extended above the delta range.. This observation is consistent with 1/f

distribution of power fluctuations of spontaneous brain activity and could be a result of a concomitant decrease in signal-to-noise ratio of LFP fluctuations and decrease of correlation magnitude with increasing frequency. However, BLP envelope correlations were significantly stronger correlates than LFPs, most notably in a previously undescribed broad alpha range. These results indicate that amplitude signals exhibit robust long-range correlations (coherent BLP envelopes) at low and high frequencies, but field potentials only exhibit strong correlations (coherent LFP phase) at lower frequencies. Thus far, these observations are consistent with studies using higher density recordings in invasive animal studies (Leopold et al., 2003).

Surprisingly, the relationship between carrier/envelope BLP frequencies and correlation magnitudes were not observed to be monotonic as might be implied by Leopold et al. Instead, correlation magnitudes and BLP:fMRI correspondence spectra showed focal frequency structure with preference for the alpha and gamma frequency ranges. Does the intermediate frequency range, a correlation "dead-zone" at 25-50 Hz, represent something special, or is it the trivial result of system employing two principle frequency ranges with a gap of activity in between?

5.4.3 The Frequency Dead Zone

Figure 5.10C summarizes the phenomenology present in ECoG correlations by plotting, at each frequency, the estimated dimensionality of the correlation matrix vs. the average ECoG:fMRI correspondence across all electrodes in a subject very similar to the group average. Overall, there was a negative correlation between ECoG:BOLD correspondence and dimensionality - frequencies with fewer, broader components were more similar to the correlations of fMRI (which are generally large in spatial scale). The figure reveals three domains of phenomenology. We suggest that a combination of high ECoG:BOLD correspondence and a low number of components is the space in which RSN-like electrophysiologic correlations are represented. Low correspondence with a low dimensionality appears indicative of structured noise in the data, such as frequencies with very low signal to noise ratio (as well as 60 Hz line noise and harmonics, not depicted). However the third region, of unknown physiologic significance, was found at frequencies with a high dimensionality and low ECoG:fMRI correspondence, specifically in the 25-50 Hz range.

There are multiple possible interpretations for the lack of correspondence in the 25-50 Hz range. There may indeed simply be an absence of correlated activity in this frequency range, or these fluctuations could be correlated only very locally. This could account for the weak correlations seen across the electrode grid (see Figure 5.7B). Whereas the alpha and high gamma frequency ranges produce correlation matrices consisting of large, broadly connected modules, this 'dead zone' would produce sparse correlation matrices representing fractured topographies with small modules, resulting in high dimensionality estimates (see Figure 5.10B). It is also possible that the geometry of currents in this frequency range may render them invisible to ECoG (e.g. lateral currents). Activity in this range could also be of the wrong scale, for example a highly local fluctuations representing within-column process not visible to ECoG electrodes.

The physiological significance of ECoG dimensionality peaks deserves further investigation, especially in relation to behavioral states. In other words, how, if at all, does the brain make of this frequency range, and do tasks activate this frequency "dead zone?" The overwhelming preponderance of electrophysiologic task activiation studies report power changes in the alpha or beta range as well as high gamma. For low frequencies alpha (8-12 Hz) power is suppressed during performance of motor (Pfurtscheller and Lopes da Silva, 1999) and perceptual/attentional tasks (Klimesch, 1999, Sauseng et al., 2009), i.e., extrinsic functions, whereas theta (4-8 Hz) power is induced by executive control (Sederberg et al., 2003), working memory (Raghavachari et al., 2001, Bastiaansen et al., 2008) and episodic memory tasks (Fell et al., 2011), i.e., intrinsic functions. Gamma activations are ubiquitously observed in ECoG responses to a wide variety of task paradigms (Ramot et al., 2012, Qian et al., 2013, Miller et al., 2014). We will specifically relate the frequencies of resting state correlations to task activations and de-activations in Chapter 7.

5.4.4 Spectral Variability in ECoG:fMRI Correspondence

The present work does not address how the major spectral features of this work (Figure 5.8) change throughout the brain. The present results are averages, thus only broadest features are represented. Similarly, the interfrequency correlations shown in Figure 5.9 reflect only the broadest features in the data. These features may change as a function of brain region or network. It has been demonstrated that the intrinsic spectral content of resting state ECOG fluctuations varies across brain regions (Groppe et al., 2013). Additionally, the frequency providing maximal phase-amplitude coupling has been shown to vary across functional systems (Foster and Parvizi, 2012).

Based on these studies, we expect that the ECoG:fMRI correspondence features to vary throughout the brain. More sophisticated approaches at spatially differentiating these features, especially as regards resting state networks, are the topic of Chapter 6.

5.5 References

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Chapter 6: Resting state electrophysiology links classic brain rhythms with hierarchical functional systems

Carl D. Hacker, B.S.E.; Abraham Z. Snyder, Ph.D., M.D.; Mrinal Pahwa, B.S.; Maurizio Corbetta, M.D.; Eric C. Leuthardt M.D.

Author Contributions

E.C. performed surgical procedures. C.D.H., A.Z.S., and M.P. analyzed data. C.D.H., A.Z.S., M.C., and E.C.L., designed the study and wrote the paper.

Abstract

Resting state functional MRI (R-fMRI) studies have shown that slow (< 0.1 Hz), intrinsic fluctuations of the blood oxygen level dependent (BOLD) signal are temporally correlated within hierarchically organized functional systems known as resting state networks (RSNs)(Doucet et al., 2011). Most broadly, this hierarchy exhibits a dichotomy between an "extrinsic" system (associated with spatial attention(Corbetta and Shulman, 2002) and sensory-motor behavior(Golland et al., 2007)) and an "intrinsic" system (associated with episodic memory(Buckner et al., 2008), executive control(Fedorenko et al., 2013), and social cognition(Adolphs, 2009)). The electrophysiological correlates of this dichotomo remain unknown. We measured the correspondence between electrocorticographic (ECoG) band-limited power (BLP) and R-fMRI correlation patterns in awake, resting, human subjects, and found theta (4-8 Hz) frequency specificity within the intrinsic system and alpha (8-12 Hz) specificity within the extrinsic system. These findings link the spectral specificity of task-based electrophysiologic responses(Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999) with the hierarchical organization of RSNs revealed by R-fMRI, and are consistent with the phylogenetically ancient, anatomical distinction between the cortico-hippocampal vs. the thalamo-cortical systems.

6.1 Introduction

Intrinsic brain activity has emerged as a major focus of systems neuroscience research(Raichle, 2009). Resting state, i.e., task-free, functional magnetic resonance imaging (RfMRI) currently is the primary technique used in the investigation of intrinsic brain activity(Smith et al., 2013). On the basis of R-fMRI studies, it is now established that slow (< 0.1 Hz), intrinsic fluctuations of the blood oxygen level dependent (BOLD) signal are temporally correlated within spatially distributed functional systems whose topography recapitulates patterns of activity during active behavior(Smith et al., 2009). The associated topographies are known as resting state networks (RSNs) or, equivalently, intrinsic connectivity networks (ICNs)(Zielinski et al., 2010).

Although it is generally assumed that there exist electrophysiological correlates of RSNs, the fundamental nature of these relations remains uncertain(Scholvinck et al., 2013). Electrocorticographic (ECoG) recording on the surface of the brain provides a means of studying the electrophysiologic correlates of RSNs at a temporal resolution inaccessible to fMRI. Taskbased studies in primates(Goense and Logothetis, 2008) as well as humans(Koch et al., 2009, Miller et al., 2014) suggest that the most robust electrophysiological correlate of the BOLD fMRI signal is wide band power, nominally in the range of 40-150 Hz. This principle has been assumed to extend to the resting state. Indeed, prior resting state ECoG studies demonstrate a correspondence between gamma (nominally, 70-110 Hz) band-limited power (BLP) timeseries correlations and R-fMRI RSNs(He et al., 2008, Keller et al., 2013). However, correspondence of BLP timeseries correlations to fMRI RSNs has so far not been systematically evaluated at lower frequencies.

A fundamental property of fMRI RSNs is that they are hierarchically organized, and that their nested structure is divided at the highest level between two 'systems', often referred to as the "extrinsic" vs. "intrinsic" systems (Doucet et al., 2011). The intrinsic system is concerned with episodic memory (Buckner et al., 2008) executive control (Fedorenko et al., 2013), and social cognition (Adolphs, 2009) whereas the extrinsic system instantiates spatial attention(Corbetta and Shulman, 2002) and sensory-motor interactions with the environment (Golland et al., 2007). It has been observed that, both at rest and during task performance, these systems are negatively coupled (Shulman et al., 1997, Fox et al., 2005). This negative coupling has been interpreted as reflecting reciprocal inhibition between externally vs. internally directed cognition.

Electrophysiology experiments have identified oscillatory responses specifically associated with "extrinsic" vs. "intrinsic" functions: alpha (8-12 Hz) power is suppressed during performance of motor (Pfurtscheller and Lopes da Silva, 1999) and perceptual/attentional tasks (Klimesch, 1999, Sauseng et al., 2009), i.e., extrinsic functions, whereas theta (4-8 Hz) power is induced by executive control (Sederberg et al., 2003), working memory (Raghavachari et al., 2001, Bastiaansen et al., 2008) and episodic memory tasks (Fell et al., 2011), i.e., intrinsic functions. Thus, the systems instantiating distinct cognitive functions generate task-induced electrophysiological responses with separable spectral content.

Here, we test the hypothesis that the spectral specificity of task-induced electrophysiological responses to "extrinsic" vs. "intrinsic" tasks is also present in resting state activity. We compare the large-scale spatial topography of spontaneous temporal correlations computed with ECoG and fMRI signals. We evaluate this comparison across ECoG frequencies and brain regions to test the hypothesis that the frequencies of maximal ECoG:fMRI correspondence are specific to the extrinsic vs. intrinsic systems.

6.2 Methods

6.2.1 Participants

All participants were patients at Barnes Jewish Hospital or St. Louis Children's Hospital with drug-resistant epilepsy undergoing electrocorticographic (ECoG) monitoring to localize seizure foci. All participants provided informed consent with oversight by the local Institutional Review Board in accordance with the National Institutes of Health guidelines and the ethical standards of the Declaration of Helsinki. Participants were selected from a large ECoG database in which least 4 days of clinical ECoG recordings as well as pre-operative structural and functional MRI and post-implant X-ray computed tomography (CT) images were acquired (n=25). Six subjects passed stringent electrophysiologic and imaging quality control criteria (described below) for inclusion in the study. See Table 6.1 for subject profiles.

6.2.2 Image Acquisition and Preprocessing

Structural and functional imaging was performed with a 3T Tim Trio Scanner (Siemens, Erlangen, Germany) using product sequences. Functional images were acquired using a BOLD contrast sensitive gradient echo echo-planar sequence (parameters) during which participants were instructed to fixate on a visual cross-hair, remain still and not fall asleep. Anatomical imaging included one sagittal T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) scan (T1W) and one T2-weighted scan (T2W).

fMRI preprocessing proceeded as previously described (Hacker et al., 2013) with the addition of image distortion correction using the FUGUE module in FSL (Jenkinson et al., 2012). Field maps were approximated using the technique described by Gholipour and colleagues (Gholipour et al., 2008). Distortion correction and motion correction were combined in one resampling step to generate volumetric time-series in Talairach atlas space (3 x 3 x 3 mm³ cubic voxels).

Additional preprocessing in preparation for FC analyses included motion censoring based on the DVARS (temporal derivative of RMS BOLD signal across voxels) measure (Smyser et al., 2010, Power et al., 2012). Motion censoring was computed before de-noising to avoid FC analyses of frames (volumes) with "cosmetically" improved DVARS values but retained artifact (Power et al., 2014). The DVARS censoring threshold was set at 0.5% root-mean-square frameto-frame BOLD signal change (Power et al., 2014) following 20 mm spatial pre-blur in each direction. Epochs containing fewer than 10 contiguous frames meeting the DVARS criterion were excluded from the functional connectivity computations. The fraction of censored data from each participant is listed in Table 6.1.

Following motion censoring, the retained frames were made zero-mean within each voxel but the data were not otherwise temporally or spatially filtered. Initial de-noising was accomplished using a strategy similar to CompCor (Behzadi et al., 2007). Nuisance regressors were derived from white matter and ventricle masks, segmented in each individual using FreeSurfer (Fischl, 2012), then spatially resampled in register with the functional data. Nuisance regressors also were extracted from voxels in the extra-axial CSF space exhibiting high (> 2.5%) temporal standard deviation. Nuisance regressors also were derived from rigid body head motion correction. Following nuisance regression, the volumetric timeseries were further de-noised using an ICA regression approach. Because of the small number of subjects (n=6) in this study, components for all subjects were manually classified according to established criteria (Kelly et al., 2010). Unambiguously artifactual components were eliminated by linear regression. The global signal averaged over the whole brain and its temporal derivative was removed by linear regression (see (Keller et al., 2013), for discussion of GS regression in ECoG:fMRI comparisons). fMRI timeseries were prepared for comparison to ECoG data by ribbonconstrained volume to surface resampling using the Human Connectome Project pipeline (Glasser et al., 2013).

Resting state network topographies were computed in each subject using a supervised classification method (Hacker et al., 2013). Briefly, this technique employs a neural network (specifically, a multi-layer perceptron performing non-linear regression) that has been trained to associate correlation maps of a standard set of task-derived seed regions with pre-defined RSN labels. We classified seed-based fMRI correlation maps generated at every brain locus to produce RSN topographies throughout the brain.

See Chapter 2 for information on Electrode Registration and Sampling BOLD Data to Electrodes

6.2.3 ECoG Data Acquisition and Preprocessing

Implanted electrodes (platinum, 4 mm, 2.3 mm exposed, PMT corporation) were 8x8 or 6x8 grids (with 1 cm spacing) and strips (1x4, 1x6, or 1x8), placed subdurally facing the cortical surface. A separate strip facing the skull served as ground and reference for the amplifier (Proamp, Lamont Medical Inc). Data were screened for channels with excessive noise and epochs with excessive environmental noise across all channels. Channels exhibiting inter-ictal activity also were excluded.

ECoG signals were referenced to a common average. A de-spiking function, $f(x) = A * \operatorname{atan} (x/A)$, where *A* is 5 s.d. of the signal, was applied to attenuate transient artifacts from medical devices (e.g., IV pumps). Data were further inspected for artifact in the timefrequency domain. Ictal events were identified by clinical staff. Sleep epochs were defined behaviorally with video records. Additionally, periods of sustained delta power (> 20% power in the 0.5-4 Hz range) were identified as slow wave sleep (SWS) and excluded. The present ECoG:fMRI analyses include only ECoG recordings at least 30 minutes separated from behaviorally identified sleep (from video recordings) or electrophysiologically identified SWS. ECoG data recorded up to 2 hours following ictal events also were excluded.

ECoG signals were decomposed into frequency components by zero-phase digital filtering using a 2nd order Butterworth filter in the forward and reverse directions (effectively, 4th order). Frequency bin edges were logarithmically spaced with cut-off frequencies at 2^k,

where k ranges from 0 to 7 in increments of 0.1. Filtered signals were squared to produce instantaneous power, then further band-pass filtered to isolate specific envelope frequency components. For a given carrier frequency, envelopes were filtered with logarithmically spaced bins with edges defined by 2^k, where k ranges from -2.5 to 1.25 in increments of 0.25. For each carrier frequency, the upper limit for envelope frequencies to be analyzed was defined as by the bin width used to filter the carrier.

6.2.4 BOLD-ECoG Comparison Methodology

Correlation maps were computed as the Pearson product-moment correlation across all pairs of electrode timeseries, treating the fMRI and ECoG BLP timeseries identically. Correlations of both ECoG and BOLD signals are systematically greater at shorter distances. Locally increased correlations may be induced by spatial smoothing of BOLD data or volume conduction of deep source in ECoG data. However, distant dependent correlations are expected to be largely driven by true physiologic correlation. Such systematic correlation:distance relationships increase the apparent similarity of ECoG and BOLD correlation maps and therefore decrease the sensitivity of ECoG:fMRI spatial correlations to topographically specific features. The inverse relation of correlation to distance can artifactually introduce long-distance correlations if the distance dependence is removed by linear regression. Thus linear distance regression can generate spurious similarity between ECoG and BOLD correlation maps. Therefore, to maximize sensitivity to RSN topography, the correlation:distance relationship was removed using B-spline regression (see Extended Data Figs. 4 and 5). After removal of the correlation:distance relationship using B-spline regression,

ECoG:fMRI correspondence was computed as the Fisher z-transformed spatial correlation of the ECoG band-limited power (BLP) and fMRI correlation maps. This procedure was computed parametric in carrier and envelope frequency, thereby producing carrier frequency × envelope frequency correspondence spectra for each electrode (e.g., Fig. 6.1C). As a final step, correspondence spectra were smoothed with a moving average filter (span of 5 bins) in log frequency space.

Participants			BOLD Data		ECoG Data		Electrode Inclusion		
Patient	Sex	Age	r-fMRI Data (mins)	Frames Rejected	ECoG Data (mins)	Epochs	Total	Rejected (Imaging)	Rejected (Ephys)
PT1	F	14	66.0	5.9%	135.6	5	100	24	0
PT2	Μ	15	73.3	4.9%	387.6	19	116	18	4
PT3	Μ	19	58.7	3.6%	703.1	15	88	2	0
PT4	М	19	44.0	3.3%	194.0	5	64	0	3
PT5	Μ	55	54.9	5.2%	293.0	6	84	7	2
PT6	F	12	62.2	14.3%	241.0	10	70	12	3
Average: 22		22	60	6.2%	326	10	87	11	2

 Table 6.1. Patient characteristics and experimental data.

6.3 Results

To enable direct comparison of resting state ECoG vs. BOLD fMRI temporal correlations, preprocessed fMRI timeseries (see Methods) were projected onto the brain surface and resampled at electrode loci (see Extended Data Figs. 1, 2, and 3). Surface-to-electrode BOLD signal resampling was computed according to the expected electrophysiologic contribution of each surface locus modeled as a transcortical dipole. ECoG signals were referenced to the common mean (excluding noisy and ictal electrodes) and band-pass filtered at logarithmic intervals to isolate particular carrier frequencies; these band-limited signals were squared and then filtered to isolate specific modulation frequencies of the BLP signal derived from a given carrier frequency band (see Methods for further details). Pearson product-moment temporal correlations were computed for all electrode pairs, treating the fMRI and ECoG BLP timeseries identically. ECoG:fMRI correspondence was computed as the spatial correlation of the ECoG BLP temporal correlations and fMRI RSNs. Thus, for each seed electrode, the ECoG:fMRI correspondence spectrum was assessed as a function BLP carrier and modulation frequency.



Figure 6.1. Spatial correspondence of ECoG and fMRI correlation maps in a single subject. A. Seed-based fMRI correlation map for a seed region (white circle) within the fronto-parietal control system (FPC). The correlation map rendering is limited to regions with electrode coverage. B. Seed-based ECoG BLP correlation maps for the same seed location as in A. C. ECoG:fMRI correspondence assessed by spatial correlation of (A) and (B), parametric in ECoG BLP carrier and modulation frequencies. Colored circles indicate frequencies for exemplars in (B). Note that ECoG correlation maps for theta and gamma frequencies for this seed region in (B) are similar to the fMRI correlation map in (A). Bottom half (D,E,F) illustrates results as per A,B,C for a seed region in the dorsal attention network (DAN). Note that correlation maps for the DAN seed at alpha (rather than theta) and gamma frequencies (E) are similar to the fMRI correlation maps and gamma frequencies (E) are similar to the fMRI correlation maps for the solution frequencies (E) are similar to the fMRI correlation maps for the dorsal attention network (DAN). Note that correlation maps for the DAN seed at alpha (rather than theta) and gamma frequencies (E) are similar to the fMRI correlation maps in (D). The frequency specific ECoG:fMRI similarity produces complimentary peaks of spatial correlation in the theta and alpha ranges in panels C and F, respectively.

Exemplar results are shown in Figure 6.1. Panel A shows the fMRI correlation map

obtained with a seed electrode overlying the middle frontal gyrus, a locus within the fronto-

parietal control RSN, which is a component of the intrinsic system. Positive correlation is

observed with signals in lateral parietal cortex (frontoparietal control network) and superior frontal cortex (default mode), and negative correlation with precentral/postcentral cortex (motor), and intraparietal sulcus (dorsal attention). Panel B shows the corresponding ECoG BLP seedbased correlation maps obtained with the same seed at different carrier frequencies. As is evident in panels A and B, the topography of theta and gamma but not alpha BLP correlations was spatially similar to the topography BOLD fMRI temporal correlations. A quantitative summary of these findings is presented Fig. 6.1C, which shows the ECoG:fMRI correspondence spectrum (across carrier × modulation frequencies). ECoG:fMRI correspondence was modestly dependent on modulation frequency but strongly dependent on carrier frequency. Thus, BLP spectral specificity appears in the carrier \times modulation display as broad horizontal bands with peaks within the high gamma (50-100 Hz) and theta bands (4-8 Hz). Panels D-F illustrate complementary results, obtained with an electrode seed overlying the frontal eye field (FEF), a locus within the dorsal attention RSN, a component of the extrinsic system. This locus showed strong ECoG:fMRI correspondence with alpha (8-12 Hz) and gamma but not theta frequencies. Thus, both seeds exhibited similar resting state BOLD fMRI and BLP correlation topographies at high gamma frequencies. Intrinsic vs. extrinsic spectral specificity was observed at theta and alpha BLP frequencies, respectively.



Figure 6.2. ECoG:fMRI correspondence spectra vary according to RSN.

Results shown for the same subject as Figure 6.1. A. RSN nodes defined within-subject by supervised classification of fMRI signal correlation patterns. B. ECoG:fMRI correspondence spectra averaged across electrodes within each node (grey traces: individual electrodes, thick line: within-node electrode average). C. Top: Correspondence spectra aggregated over SMN and FPC networks. Bottom: Correspondence spectra after linear detrending. Note a predominance FPC peaks at 6 Hz and SMN peaks at 9 Hz. Black bar indicates range of frequencies used to compute correlations in D. D. Correspondence spectrum similarity across electrode pairs computed by linear correlation over the 4-13 Hz range. SFG: superior frontal gyrus (DMN); MFG: middle frontal gyrus (FPC); FEF: frontal eye field (DAN); CS: central sulcus (SMN); IPS: intra-parietal sulcus (DAN); IPL: inferior parietal lobule (DAN)

Figure 6.2 extends the analysis shown in Figure 6.1 to include all electrodes in one subject. The cortical surface was parcellated into seven RSNs according to our previously reported scheme(Hacker et al., 2013). RSNs generally are comprised of spatially discontiguous regions (nodes). For example, the fronto-parietal control (FPC) RSN includes five distinct nodes within the illustrated cortical surface (color coded yellow in Fig. 6.2A). Thus, each electrode was assigned to one node of one RSN. Correspondence spectra were averaged across electrodes within each node. The results of this analysis (Fig. 6.2B) reveal the dependence of ECoG:fMRI correspondence on RSN. High correspondence in the gamma frequency range (nominally, above 45 Hz) is ubiquitous. Low correspondence is generally observed in the beta frequency range (nominally, 13-45 Hz). At lower BLP frequencies, the frequency of maximal correspondence depends on RSN. Thus, components of the dorsal attention network (DAN; dark blue in Fig. 6.2A) exhibit high correspondence in the low-alpha range (8-10 Hz), whereas components of the fronto-parietal control (FPC; yellow in Fig. 6.2A) RSN exhibit maximal correspondence in the theta range (4-8 Hz).

The results in Fig. 2B suggest that the fine features (locations of peaks and troughs) of ECoG:fMRI correspondence spectra differ according to RSN in the 4-13 Hz range. To quantitate this observation, we computed a numerical index of correspondence spectrum similarity for all electrode pairs. Specifically, the correspondence spectrum at each electrode was detrended as illustrated in Fig. 6.2C and the Pearson correlation was computed over logarithmic frequency bins in the 4-13 Hz range. The electrode-pair matrix result, shown in Fig. 6.2D, demonstrates similarity of spectral features at the highest level of the RSN hierarchy. Thus, high similarity was found between all electrodes within the DAN and the sensorimotor network (SMN; extrinsic

system). High similarity was found between all electrodes within the FPC and the default mode network (DMN; intrinsic system). In contrast, low similarity was found for electrodes paired on opposite poles of the hierarchy, e.g., DAN:DMN.



Figure 6.3. Average ECoG:fMRI Correspondence Spectra

A. ECoG:fMRI corrspondence spectra averaged within RSNs across all electrodes and all subjects. B. Detrended ECoG:fMRI spatial correlation spectra averaged within RSNs. Each trace corresponds to an individual participant. C. Correlation between RSN-averaged detrended spectra shown in panel (B), averaged across participants. Higher correlation (red hues) indicates greater similarity of RSN-specfic spectral features. D. Distributions of inter-RSN spectral correlations over subjects. Within each box plot the red line indicates the inter-subject median, the blue box indicates inter-quartile range, and whiskers: range. Asterisk indicates significant t-test for greater within system vs. across system RSN spectral correlations.

To examine the extrinsic vs. intrinsic system dichotomy at the group level, ECoG:fMRI correspondence spectra were averaged over electrodes within RSNs in all six subjects satisfying rigorous QA criteria (see Methods). Averaged RSN-specific spectra revealed convincing systemspecific features (Fig. 6.3A). The extrinsic system (DAN and SMN) mean spectrum peaked at 9 Hz. The intrinsic system (DMN and FPC) mean spectrum peaked at 7 Hz. These differences in peak loci also were consistently obtained at the single subject level by averaging detrended correspondence spectra over electrodes within each RSN (Fig. 6.3B, and see also Fig. 6.4D). The similarity of RSN-specific spectra within and across systems was evaluated for each subject as the Fisher z-transformed Pearson correlation over log frequency spanning 4-13 Hz. The spectral similarity measures then were averaged over subjects to obtain the group-level results shown in Fig. 6.3C. These results clearly reveal a block structure corresponding to the extrinsic vs. intrinsic system dichotomy. Distributions over subjects of the RSN:RSN similarity measures are shown in Fig. 6.3D. Within-system correlations (average of DAN:SMN and FPC:DMN) were systematically higher than across-system correlations (average of DAN:DMN, DAN:FPC, SMN:DMN, and SMN:FPC), (p<0.0001, one sided t-test).



Figure 6.4. System-level spectral specificity of ECoG correlations.

A. Correspondence spectrum averaged across all electrodes overlying intrinsic system RSNs (average over all subjects). Note similarity of spectral features in carrier domain to exemplar in Fig. 6.1C. B. Correspondence spectrum average for all extrinsic system electrodes in the same format as (A). Note similarity to Fig. 6.1F. Also note that (A) and (B) exhibit a gamma peak at the same frequency, but different peaks for low frequencies: 9-10 Hz for the extrinsic system average vs. 6-7 Hz for the intrinsic system average. C. Correspondence spectra collapsed over the 0.1-1 Hz modulation frequency range for both systems. Note offset of peaks in the theta and alpha range. D. Peak frequencies for individual within-subject system averages. Each marker represents the peak frequency in the 4-13 Hz range for one subject. Note systematically greater extrinsic peak frequency in all subjects.

Figure 6.4 shows extrinsic and intrinsic system correspondence spectra averaged over all subjects. These results demonstrate, at the group level, the principle features illustrated in Figure 6.1: ECoG:fMRI correspondence depends only modestly on modulation frequency but is sharply

structured in relation to carrier frequency (panels A and B). The extrinsic and intrinsic systems both exhibit high ECoG:fMRI correspondence in the gamma (> 50 Hz) carrier frequency range and a trough at approximately 35 Hz (panel C). Most importantly, extrinsic vs. intrinsic carrier specificity is most marked in the 4-13 Hz range, i.e., in the theta and alpha bands.

6.4 Discussion

6.4.1 Frequency specificity of fMRI RSNs

Our results concern the spectral dependence of the spatial correspondence between fMRI and electrophysiologic correlation patterns. High ECoG:fMRI correspondence was observed for high-gamma BLP (60-100 Hz) and low frequency BLP (<25 Hz, maximal within the 4-13 Hz range) and a minimum of correspondence was observed for low-gamma frequency BLP (25-50 Hz). The high-frequency (gamma) BLP results are consistent with previous studies comparing the topography of temporal correlations across ECoG and BOLD fMRI in the same subjects (He et al., 2008, and Keller et al., 2013). We extend these findings by revealing previously undescribed correspondence at lower BLP frequencies (4-25 Hz). Thus, our results demonstrate that ECoG:fMRI correspondence occurs in two distinct spectral regimes in resting state brain activity. These regimes recall the association of gamma synchronization together with low-frequency desynchronization, which features are ubiquitously observed in ECoG responses to a wide variety of task paradigms (Ramot et al., 2012, Qian et al., 2013, Miller et al., 2014). While these task-induced responses are opposite in sign, spatial correspondence spectra (Figs. 1 - 3) are positive for both frequency regimes. This apparent discrepancy can be reconciled if it is
hypothesized that comparable BLP dynamics occur in both task and rest conditions. Specificially, simultaneous increases as well as decreases of spontaneous BLP power within RSNs are expected to produce positive temporal correlations which, in turn, produce ECoG:fMRI spatial correspondence at their respective frequencies.

6.4.2 Intrinsic electrophysiological activity differentiates the intrinsic vs. extrinsic systems

Importantly, regional specificity was observed in the low frequency regime. Specifically, correspondence in the alpha (8-12 Hz) and theta (4-8 Hz) bands was found within the extrinsic and intrinsic functional systems, respectively. These spectral associations are well documented in both task-based, non-invasive EEG (Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999) and invasive ECoG studies (Sederberg et al., 2003, Miller et al., 2007), but heretofore have not been reported in spontaneous activity. We show that these spectral features, which have been previously associated with specific cognitive domains, are topographically linked to RSNs known to instantiate extrinsic vs. intrinsic functionality. We note that task engagement of the intrinsic system *enhances* theta oscillations whereas engagement of the extrinsic systems *suppresses* alpha oscillations (Klimesch, 1999). However, either effect, occurring synchronously within a distributed functional system, is expected to generate BLP temporal correlations consistent with the present results. Thus, this study links the topographies of the extrinsic vs. intrinsic functional systems (and by extension, their associated cognitive domains) with spatially segregated alpha (8-12 Hz) vs. theta (4-8 Hz) intrinsic oscillatory activity.

These results are consistent with the phylogenetically ancient, anatomical dichotomy between the cortico-hippocampal vs. the thalamo-cortical systems. Theta rhythms are organized in the hippocampus (Buzsaki, 2002), a structure associated with the default mode network, a core component of the intrinsic system (Buckner et al., 2008). Moreover, the hippocampus is anatomically connected primarily with prefrontal and parietal higher-order association cortices, as opposed to primary sensory-motor areas (Lavenex and Amaral, 2000). In contradistinction, alpha rhythms are generated by thalamo-cortical circuits (Suffczynski et al., 2001) and are most clearly recorded over primary sensory-motor areas (Pfurtscheller and Lopes da Silva, 1999), structures associated with extrinsic functions. Thus, the present results add an electrophysiologic dimension to the dichotomy between the intrinsic vs. extrinsic functional systems defined by RfMRI.

6.4.3 Relation to BOLD fMRI Frequencies

For BLP envelopes derived from both low (theta/alpha) and high (gamma) frequency carrier waves, maximal ECoG:fMRI correspondence was observed at envelope modulation frequencies centered slightly above 0.1 Hz (Figure 6.4 A and B). This peak extended broadly from 0.01 Hz to 1 Hz for both theta/alpha and gamma BLP correlations. This modulation frequency range is consistent with that found by Keller and colleagues for gamma BLP, but is above the range of coherent BOLD fMRI fluctuations responsible for resting-state network correlations, which extends up to but not beyond 0.1 Hz (Chang and Glover, 2010, Keller et al., 2013). The apparent spectral discrepancy between ECoG BLP envelope frequencies and BOLD coherence probably represents the low-pass filter characteristics of the BOLD hemodynamic response function acting on electrophysiology that extends to slightly higher frequencies (Hathout et al., 1999, Anderson, 2008).

6.4.4 Cross-frequency Coupling

Phase-amplitude coupling (PAC), i.e., amplitude modulation of fast electrophysiological activity by the phase of slower activity, is increasingly recognized as a fundamental organizing principle of the brain's electrical activity (Canolty and Knight, 2010, Jiang et al., 2015). PAC classically refers to the modulation of gamma amplitude by the phase of theta or alpha frequency oscillations, which is thought to control the tight modulation of excitability on the timescale of stimuli and behavioral responses. The present results indicate that infra-slow fluctuations of intrinsic electrophysiological rhythms in the paired theta/gamma as well as alpha/gamma frequency ranges are specific to the intrinsic and extrinsic functional systems, respectively. These findings coincide with the spatio-spectral organization of PAC in spontaneous activity: Foster and colleagues reported that theta-gamma coupling was strongest within the posterior precuneus cortex (PCC) whereas alpha-gamma coupling was strongest within primary visual cortex (Foster and Parvizi, 2012). The PCC is a core component of the DMN, an intrinsic system network, whereas visual cortex is a component of the extrinsic system.

PAC and the presently reported infra-slow amplitude envelope correlations represent manifestations of spatio-spectral specificity at two different time-scales. PAC concerns gamma power modulations on a timescale of 100-200 ms, whereas our results concern the modulation of the amplitude of both low and high frequency oscillations on the much longer (5-10 s) infra-slow timescale. However, infra-slow activity may modulate gamma activity as a result of recursive hierarchical nesting, whereby infra-slow activity modulates theta/alpha waves which, in turn, modulate gamma activity (Lakatos et al., 2005). Indeed, the spatio-spectrally specific PAC reported by Foster and colleagues was itself modulated by a infra-slow (~0.8 Hz) fluctuation.

6.4.5 Methodological Considerations

Our work incorporates several methodological innovations in the comparison of ECoG and fMRI data that may account for enhanced detection of spectral differences between systems. Single subject resting state fMRI is technically challenging because of the limited signal to noise ratio and high prevalence of head motion (Hacker et al., 2013). We addressed these challenges by extended fMRI data acquisition times (average 60 minutes), exclusion of fMRI volumes contaminated by head motion from computation of correlations (Power et al., 2012), and additional removal of structured noise using ICA (Griffanti et al., 2014) (see Supplemental Figure 6.S1). In contrast to previous ECoG:fMRI studies, anatomical registration of fMRI data included compensation for echo planar imaging-related distortions (Gholipour et al., 2008). To improve registration of fMRI data with electrodes, we incorporated knowledge of the local cortical surface geometry in weighting the contribution of fMRI signal at each electrode. Electronic fMRI noise was reduced by geodesic smoothing on the cortical surface (Glasser et al., 2013). These maneuvers, in combination, reduced cross-gyral contamination and improved spatial specificity while preserving the fMRI signal to noise ratio.

Correlations of both electrophysiologic and fMRI signals are systematically greater at short distances (He et al., 2008) (see Extended Data Figures 6.4 and 6.5). Although these local correlations may, in part, be attributed to spatial smoothing of the BOLD fMRI data or volume

conduction of sources in ECoG data, they most likely reflect true physiologic correlation (Leopold et al., 2003). A systematic relation between correlation and distance is present in fMRI data as well as ECoG at all BLP frequencies. This relation necessarily increases the apparent spatial similarity of ECoG and BOLD correlation maps because local correlations dominate the fine spectral differences in ECoG:BOLD correspondence if not removed, e.g., (Liu et al., 2015). Previous attempts to control for this effect have excluded nearby electrodes or removed the relation between correlation and distance with a linear model (He et al., 2008, Keller et al., 2013). However, because correlation is inversely proportional to distance (see Extended Data Figures 6.4 and 6.5), modeling this effect as linear in distance induces artifactual long distance correlations, which may generate spurious similarity between ECoG and BOLD correlation maps. Therefore, to maximize sensitivity to RSN topography, the correlation:distance relationship was removed using nonlinear (B-spline) regression (see Extended Data Figs. 4 and 5).

6.4.6 Conclusion

We show that the temporal frequencies previously associated with task-induced responses are specifically present in the correlation structure of spontaneous electrophysiological activity within the intrinsic and extrinsic functional systems. It has previously been shown that the correlation structure of spontaneous fMRI activity recapitulates the topography of responses to specific task paradigms (Kenet et al., 2003, Smith et al., 2009). The present work suggests that this observation extends to the temporal frequency domain. Thus, based on the available evidence, we propose that spontaneously activity constrains both the spatial topography and

spectral organization of task-induced responses.

6.5 References

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Supplemental Content



Figure 6.S1. Exemplar manually classified ICA components. A. Components of neuronal origin (i.e., resting state network components). B. Artifact components of physiologic (e.g., respiratory, cardiac) or non-physiologic (e.g., head motion) origin.

Chapter 7: Relationship Between Resting State Correlations and Task-Induced Activity

The 3D reach task used in this study was designed by David T. Bundy, who acquired the data used in this chapter with the assistance of other members of the lab of Eric Leuthardt. Nicholas P. Szrama adapted the Deese, Roediger, and McDermott false memory task paradigm for ECoG and acquired data from the auditory task participants. Resting state data were acquired as described in Chapters 5 and 6. DTB and NPS contributed text describing the task designs for this chapter. All other writing and all analyses were performed by Carl D. Hacker.

7.1 Introduction

In recent years spontaneous brain activity has been a topic of intense interest in neuroscience, with an exponentially increasing yearly rate of publications (Snyder and Raichle, 2012). However, the functional and physiological roles of spontaneous activity remain incompletely understood. Spontaneous electrophysiologic activity is known to be correlated throughout large-scale functional systems (He et al., 2008, Nir et al., 2008, Keller et al., 2013); see also Chapters 5 and 6. Does this activity reflect unconstrained cognition, or represent some other process?

The timescale of functional connectivity, whether observed with fMRI, slow cortical potentials, or band-limited power envelopes (Keller et al., 2012) is much slower (0.01-1 Hz) than that of traditional behaviorally-relevant oscillatory frequencies (3-150 Hz) (Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999). However, new evidence has shown us that spontaneous activity at the infra-slow timescale can affect behavior, by biasing perception (Sadaghiani et al.,

2010) or motor performance (Fox et al., 2007). Additionally, phase-amplitude coupling allows for the possibility of very slow rhythms to influence faster activity in a behaviorally significant manner (Canolty and Knight, 2010). Insight into the significance of spontaneous activity may be found by in its relation to task-related activity, which has been better characterized and is more directly relatable to cognitive function.

The majority of studies on the correspondence between spontaneous activity and task responses have incorporated resting state fMRI and task fMRI. It is widely believed that BOLD responses reflect underlying neurophysiology convolved with a slow hemodynamic response function; as a result fMRI responses have effectively no spectral content below 0.1-0.2 Hz (Hathout et al., 1999, Anderson, 2008). Therefore, task vs. rest comparisons have not generally not studied relationships between temporal dynamics or spectral content. Instead, these studies have shown a topographic correspondence between the spatial distributions of task activations and resting state network (RSN) topography (Smith et al., 2009, Power et al., 2011, Bertolero et al., 2015, Yeo et al., 2015).

To the best of our knowledge, no electrophysiological studies have directly compared the large-scale structure of correlated spontaneous activity to task-induced responses across frequencies. However, studies combining electrophysiology and fMRI in task-only or rest-only experiments add context to this question, especially when considered in conjunction with the fMRI task vs. rest studies described above. In humans, evoked gamma activity has been shown to spatially correspond to BOLD responses in various electrocorticography (ECoG)-based task paradigms (Brovelli et al., 2005, Jacques et al., 2015). Similar results have been found at other frequencies (Conner et al., 2011, Ojemann et al., 2013). Appropriately, evoked decreases in ECoG

gamma power spatially corresponded to the default mode network (Miller et al., 2009). In purely resting state studies, spatial correspondence with the fMRI correlation structure was found for inter-electrode correlation patterns of ECoG slow cortical potentials (He et al., 2008) and gamma band-limited power envelopes (Keller et al., 2013).

In combination, these three lines of evidence based on spatial correspondence (of resting fMRI:task fMRI; task ECoG:task fMRI; and resting ECoG:resting fMRI) suggest that strong resting ECoG:task ECoG correspondence should be evident in human recordings. Further, our findings in chapter 6 suggest that this correspondence will occur at specific frequencies: we found ECoG:fMRI correspondence in specific frequency bands including alpha (8-12 Hz) and high gamma (70-110 Hz). The exact frequency ranges varied across the cortex in a manner concordant with previously described frequency specificity in task paradigmatic responses. Therefore, in the present study we examine whether resting state ECoG BLP correlations correspond topographically to task-induced BLP responses. We hypothesize that resting state correlations exhibit task-like structure both spatially and spectrally: specifically we will investigate whether BLP correlation maps exhibit topographies similar to the spatial distributions of task-induced power changes in a frequency specific manner. In other words, we hypothesize that electrodes co-activated by a task will be temporally correlated at rest, specifically at those frequencies relevant to task responses.

7.2 Methods

7.2.1 Patients

The auditory task data were acquired from subjects performing a modified version of the Deese, Roediger, and McDermott (DRM) false memory paradigm (Deese 1959; Roediger and Mcdermott 1995). The motor task subjects performed a novel 3D reach task. Data from 3 subjects were analyzed.

7.2.2 Resting State Analyses

All methods for resting state BLP correlation maps were performed as described in Chapter 6.

7.2.3 Task Design

Reaching Task Design:

To examine the relationship between ECoG signals and reaching movements, a 3D center-out reaching task was used. Hand positions for the moving limb were collected using a Flock of Birds six degree-of-freedom motion capture system (Ascension Technology, Shelburne, VT). A single sensor was fixed to the index and middle fingers of the moving arm to track hand position. Hand positions in 3D space were sampled at 37.5 Hz. Kinematic data was recorded and synchronized with ECoG signals using a custom-programmed Flock of Birds filter that was integrated into the BCI2000 system. The center-out reaching task consisted of cued reaches to 8

targets positioned at the corners of a physical cube with 50 cm long sides that was set in front of the patient. All reaches began from a target at the center of the cube and progressed to one of the 8 corners of the cube. LED lights that were placed at the center target and each of the external targets provided patients with stimulus cues and reward feedback that was synchronized to the ECoG and kinematic recordings through a custom-built microcontroller circuit that interfaced with the BCI2000 system via a USB interface and custom-programmed BCI2000 application module. During performance of the task, patients were seated in their hospital bed in a semirecumbent position with the center target placed at the patient's midline approximately 40 cm away from their chest. To compare contralateral and ipsilateral arm movements, in four of the five patients, the task was performed using the arm contralateral to the electrode array in one session and with the arm ipsilateral to the electrode array in a second recording session.

Prior to beginning task performance, sensors were calibrated to determine the location of the target positions and to account for any limitations in patient-specific range-of-motion. Each trial began with a visual cue for patients to move their hand to the center hold position at which time a hold-A period began, lasting for 500 ms for Patient 1 and 1000 ms for Patients 2-5. During the hold-A period no other stimuli about the target for the current trial was provided. After completion of the hold-A period, a 2 second plan period began, during which time one of the external targets was illuminated and patients were instructed to plan a reaching movement to the target indicated. Patients were instructed to plan but not initiate the reaching movement and to maintain holding their hand at the center target. At the conclusion of the plan period, the indicated external target changed colors, cueing the patient to initiate a reaching movement to the external target. Upon reaching the external target, the LED at the specific target turned to green,

indicating that the patient had correctly reached the target and cueing the beginning of a 500 ms hold-B period. At the conclusion of the hold-B period, the center target and each of the 8 external targets were illuminated in green to indicate a successful trial completion. If patients reached to an incorrect target or did not reach the correct target within the 4 second time period allowed for the movement, the trial was aborted and all LED lights were illuminated in red to indicate an unsuccessful trial. In Patients 4 and 5, a trial was also aborted if the patient moved before the end of the hold-A, plan, or hold-B periods. The 8 targets were presented in a random order and patients completed multiple runs with 2-4 trials to each target for a total of 16-32 total trials per run. Ideal task performance consisted of 8 runs of 32 trials, for a total of 256 trials. The total number of trials collected and duration of each run were adjusted based upon each patient's stamina and comfort.

7.2.3.2 Auditory Task Design

This task is divided into two segments. During the first segment, subjects passively listen to auditory stimuli of real words and are instructed to remember each word in the list. Shortly afterwards, subjects are given a recognition test via auditory stimuli and patients are asked to click a mouse button if the current word being heard is either old or new (never heard before). In this study, only the passive presentation component of the task was used.

During the experiment, the patients received a brief (1 s) visual stimulus cueing the beginning of a new list (e.g., the text "LIST 1" will appear on the monitor). List 1 and List 2 were presented in succession (preceded by the appropriate visual cues denoting the list being presented), followed by a brief 2 second pause, and repetition of List 1 and List 2 in succession (again preceded by the appropriate visual cues denoting the list being presented). All study

words and critical lures were taken from a large compilation of DRM word lists (Roediger, Watson et al. 2001). Each auditory stimulus was at most 1.2 seconds long (mean=1.1s, std=145ms, range=[0.54s, 1.2s]). However, all auditory stimuli were played for 1.2 seconds and thus if a stimulus finished playing before 1.2 seconds have elapsed, the remaining duration of time was followed by silence. There was a 750 ms pause between the presentation of each of the 13 words in a list during which there was silence. Additionally, patients were instructed to maintain their eyes on a fixation cross presented on the monitor during the entirety of the task. A timeline of the task structure of the presentation phase is shown: visual cue of "LIST 1" (1 s) \rightarrow study word 1list1 (1.2 s) \rightarrow pause (750 ms) \rightarrow study word 2list1 (1.2 s) \rightarrow \rightarrow study word 13list1 \rightarrow pause (750 ms) \rightarrow visual cue of "LIST 2" (1 s) \rightarrow study word 1list2 (1.2 s) \rightarrow pause $(750 \text{ ms}) \rightarrow \text{study word 2list2} (1.2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (2 \text{ s}) \rightarrow \dots \rightarrow \text{study word 13list2} \rightarrow \text{pause} (750 \text{ ms}) \rightarrow \text{pause} (750 \text{$ s). The above timeline was repeated once after the last study word in list 2 was heard. Thus, each word in each list is heard exactly twice. One or two practice runs will be given prior to recording in order to acquaint the subjects with the task. None of the practice words will appear in the presentation or recognition phases of the task. 13 DRM lists will be presented for each patient. The total runtime for entire task with 13 DRM lists is approximately 30 minutes.

During the task, subjects will be in an semi-recumbent position on a hospital bed. A computer mouse will be placed within arm's reach of the subject during the recognition phase of the task. Subjects will be given earbud headphones to listen to auditory stimuli. For visual stimuli, a computer monitor will be placed approximately 40 cm from their face. A green fixation cross will be projected onto the monitor throughout the presentation of all stimuli.

Subjects will be instructed to keep their gaze on the fixation cross throughout the entire experiment.

Stimulus Construction:

All auditory stimuli (1114 words in total) were recorded from a female Native English speaker using a Sony ICD-SX712D Digital Voice recorder. Stimuli were recorded in a quiet environment at a 44.1 kHz sampling rate with 16 bit depth using LPCM encoding. Background noise in the recordings were reduced using maximum a posterior estimators of the non-noisy audio signal as outlined by Lu and Loizou (Lu and Loizou 2011). Two auditory recordings of every word were taken so that the auditory stimuli during the presentation phase was not identical to the auditory stimuli in the recognition phase.

7.3 Results

7.3.1 Power changes during task performance

Time-frequency plots were used to visualize the spatial, temporal, and spectral distribution of power changes in response to each task. These plots were generated by computing the median across trials of the power time series (see 7.2.4) at each frequency at each electrode. Figure 7.1 illustrates these results for all electrodes for the 3D reach task in one subject. A collection of electrodes in the superior/posterior portion of the electrode grid exhibited increased high frequency power in the move-to-center (labeled "center") and the "move to target" (hereafter referred to as "move") phases of the task (Figure 7.1A). These electrodes also exhibit high frequencies power decreases during the planning stage of the task which were accompanied by low frequency power increases. These electrodes were localized over the primary motor

cortex of this subject (Figure 7.1B). Figure 7.1C shows an expanded view of the electrode with greatest gamma power changes during the task.



Figure 7.1. Time-Frequency Analysis of ECoG Activity in 3D Reach Task

A. Each plot represents one electrode. The color scale ranges from [-1 1] inter-quartile ranges about the trial median. B. Localization of electrodes (see Chapter 2) overlaid on multi-layer perceptron-defined sensorimotor network topography (see Chapter 3). C. Expanded view of response median in one electrode. 10 and 100 indicate the frequency (in Hz). Solid bars indicate the trial start and end, with dotted lines delineating each phase of the task.

The spatial distribution of gamma activations for the reach task were similar for each of the three subjects (in each case overlying the primary motor cortex). The auditory task produced activations over the posterior temporal lobe extending anteriorly along the superior temporal gyrus. All subjects exhibited gamma frequency power increases and concomitant alpha/beta frequency power decreases in response to both the auditory and reach tasks. The relative power changes and temporal distribution of these changes are illustrated in Figure 7.2. In each case, the electrode with the largest magnitude of gamma activation was selected.





For each subject/task pair, the time-frequency distribution of power changes is illustrated for the electrode with greatest gamma frequency power changes. To summarize the power changes related to the task, the trial-median response was averaged across time. For the reach task the blue bar indicates the time range for the planning period and the red bar indicates the movement period. For the auditory task, the red bar indicates the time period for computing the auditory response. The traces to the right of each plot indicate the power changes at each frequency averaged over the corresponding time interval.

7.3.2 Relation of Task Performance to Resting State Correlations

The spatial distribution of power changes, summarized by averaging across time, are

illustrated in figure 7.3A. The electrode with the largest magnitude of responses was used as a

seed for a resting state correlation analysis. Correlation maps were produced for this electrode

for multiple frequencies (beta - 18 Hz, low gamma - 42 Hz, and high gamma 99 Hz, Figure

7.3B). The correlation values between the seed electrode and every other (paired) electrode were compared to the magnitude of the task responses at the paired electrode at the corresponding frequency. Thus, at each frequency, the task-related power change at each electrode was plotted against the correlation of that electrode and the seed electrode (Figure 7.3C). At beta frequencies, electrodes exhibiting greater power increases during the planning period were more correlated with the most activated electrode (r=0.66). During the movement period (during which beta power decreases occurred over the motor cortex) increased inter-electrode correlation was associated with greater power decreases. The high gamma BLP correlation map topographies were similar to the low frequency correlation maps, but the sign of power changes during task activations is reversed, leading to inverted relationships between resting state correlation and task activation from those described for beta frequencies.

Correlations computed in Figure 7.3C constitute spatial correlations between resting-state correlations and task activation topographies. The illustrated relationships were statistically significant at the p<0.0001 level for alpha, beta, and high gamma frequencies, and not statistically significant at the p=0.05 level for low-gamma frequencies. Task:rest spatial correlations were computed parametric in frequency from 2 to 110 Hz and summarized by a task:rest spatial correspondence spectrum (Figure 7.3D, right) for the planning and movement phases of the task. The task response spectrum for the seed electrode is reproduced for comparison in 7.3D, left.



Figure 7.3. Task:Rest Spatial Correspondence Methodology

A. Traces indicate the power changes at each frequency averaged over the time interval described in Figure 7.2 for the planning (blue) and movement (red) phases of the task. B. BLP correlation maps produced using the electrode outlined in (A) as a seed region. The color scaling for the correlation maps ranged [-.5 .5]. C. Relation between resting state correlations with the seed electrode and task response magnitudes (of the seed electrode) for beta, low-gamma, and high-gamma frequencies. D. The left panel indicates the task response spectrum for the seed electrode (cf. Figure 7.2). The center panel indicates the (spatial) correlation between resting the outlined electrode as a seed region. The right panel shows the task:rest spatial correspondence spectrum for a negative control electrode, i.e., an electrode with no task response.

Task:rest spatial correlations were computed for each of the three subjects performing the

motor task, and are illustrated in Figure 7.4 below the task response spectrum of the seed

electrode for comparison of spectral features.



Figure 7.4 Spectral Correspondence of Task Activity and Task:Rest Correspondence 3D reaching task. The top row depicts the task response spectrum for the seed electrode, i.e., the electrode with the greatest magnitude of task response (cf. Figure 7.2). The bottom row depicts the (spatial) correlation between resting correlations and task response magnitudes as a function of frequency (cf. Figure 7.3).

Inter-electrode correlations were interrogated specifically between an exemplar pair of electrodes such that both electrodes were activated by the task paradigm and correlated at rest (auditory task, Figure 7.5). The first electrode was chosen based on the magnitude of task response (the same electrode used in Figure 7.2 in each subject). Resting state BLP correlations were computed at each frequency (Figure 7.5B) and are shown alongside the spectrum task induced power changes for the seed electrode for comparison (Figure 7.5C). In PT1, the topography of alpha correlations is spare and low in magnitude, the pair-wise temporal

correlations are significantly stronger for high gamma frequencies than alpha frequencies, and the task induced activity shows predominately gamma frequencies (with faint alpha effects). In contrast, PT2 exhibits robust alpha correlations and predominately alpha power decreases in response to the auditory task.



Figure 7.5 Magnitude Scaling of Resting State Correlations and Task Activity

Auditory task. A. Resting state correlation maps. The large markers indicate the location of the seed electrode used for correlation computations. The magenta asterisk indicates the electrode indicates the paired electrode for exemplar inter-electrode correlations. B. Spectrum of correlations between marked electrodes.

7.4 Discussion

7.4.1 Spatial and Spectral Distribution of Task Responses

Both tasks in this study exhibited opposed low and high frequency responses in all tasks.

Specifically, low frequency increases and high frequency decreases in power were found in the

motor cortex in preparation for movement. The opposite case was found in motor cortex during movement and in auditory cortex during passive speech presentation: low frequency power decreases accompanied by high frequency increases. These results accord with a large body of electrophysiology studies which consistently describe similar results in responses to a wide variety of task paradigms (Ramot et al., 2012, Qian et al., 2013, Miller et al., 2014). These opposed processes are well illustrated in Figure 7.2. The presently observed antagonism of alpha and gamma processes during planning and movement are consistent with the view of alpha as representing an inhibitory thalamic influence on cortical gamma activity (Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999). These opposed frequencies appear to be occur as large scale processes within broad functional networks gamma activations. Consistent with (Miller et al., 2007), we found that low frequency phenomenology extended more broadly than that of high frequencies, especially for the auditory task (not shown). The gamma activations were spatially more distributed than those of motor movements involving specific joints in Miller et al., 2007, which is reasonable given the involvement of multiple joints in reaching movements.

Notably, responses were not observed in the low-gamma range for either task. The lack of phenomenology at these frequencies corresponds to the "dead zone" described in Chapter 5. Low gamma frequencies produced pronounced lack of resting state BLP correlations (see Figures 5.7B and 5.8).

7.4.2 Correspondence Between Resting State Correspondence and Task-Induced Activity

The results in Figure 7.3 capture the spatial distribution of power changes in response to the reaching and auditory task paradigms. These spatial patterns were most similar to resting state correlations at frequencies where the magnitudes of induced responses were high. It should

be noted that coordinated increases as well as decreases in task activity both corresponded to positive inter-electrode temporal BLP correlations (see Figure 7.3B). This substantiates the assertion in Chapter 6.4.1 that coordinated induced responses across pairs of regions in task behavior should correspond to simultaneous increases or decreases in spontaneous BLP activity. Thus, it is reasonable that task induced power *decreases* should be spatially anti-correlated with resting state correlations, as can be seen for alpha frequencies in the movement phase of the reach task and for high gamma frequencies in the planning phase in the task vs. rest correlation analysis in Figure 7.3C and D.

7.4.3 Spectral Specificity and Magnitude Scaling in Task Responses vs. Resting Correlations

The frequencies activated by paradigms in this study were similar across the reach task and the auditory task, and were grossly similar across all subjects. However, some spectral specificity is evident in the results in Figure 7.4. For example, the low alpha range (8-10 Hz) exhibited robust power increases relative to baseline in the planning phase of the reach task for PT2 (blue peak in top/middle panel). Accordingly, the task:rest correspondence spectrum also has a (modest) peak in this frequency range. In contrast, PT3 exhibited a marked absence of low alpha power during planning and also exhibited a local minimum of rest:task correspondence at the same frequency. These results suggest an alignment in the fine spectral features (relative peaks and troughs) of resting state correlations and task activations, but a larger dataset would be required show this conclusively.

Stronger evidence of similar features between task activations and resting correlations can be in the inter-individual variability of the magnitudes of these measures. An illustrative example of proportional scaling between induced power changes and resting correlations is illustrated in Figure 7.5. PT3 was a subject with remarkably alpha power, visible in raw voltage traces at rest. Mathematically, this allows for the possibility of a robust alpha event-related desynchronization in response to the auditory task. Figure 7.5B (bottom) indicates that large, coordinated modulations of alpha power were also present at rest, resulting in BLP correlations. In this subject, the resting alpha correlation was of greater magnitude than the gamma BLP correlations. PT1, on the other hand, exhibited significantly less alpha at rest; correspondingly, there was minimal task-induced change in alpha, which failed to produce alpha BLP correlations (7.5A). The gamma activations for PT1, however, dwarfed all other task-induced effects in this study. Consistent with these observations, the inter-electrode correlation spectra illustrated much stronger gamma BLP correlations than alpha BLP.

7.4.4 Implications for the Interpretation of Large-Scale Correlations of Spontaneous Activity

The findings in this study provide some evidence for the hypotheses outlined in chapter 6, i.e., that the spectral specificity of resting state correlations can be accounted for by the spectral content of behaviorally relevant fluctuations occurring at the same location. In conclusion, these data suggest that both task-related and spontaneous fluctuations are both governed by the regionally varying intrinsic oscillatory properties of the cortex. However, the present data only address half of the phenomenology presented in Chapter 6. This study is limited in that both of the task paradigms induce activity in the alpha (and beta) / high-gamma complex within the extrinsic system. A combination of intrinsic and extrinsic system tasks in the same subjects would be desirable in future studies. Electrophysiology task paradigms involving

executive control (Sederberg et al., 2003), working memory (Raghavachari et al., 2001,

Bastiaansen et al., 2008) and episodic memory tasks (Fell et al., 2011) would all be reasonable

candidates for such a study as they induce theta activity within intrinsic system structures.

7.5 References

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Chapter 8: Concluding Remarks

Recent studies of the electrophysiology of spontaneous activity can be traced to earlier research using task-based experiments to study the electrophysiologic basis of the fMRI. In a seminal study, visual stimuli were presented to non-human primates, while simultaneously measuring the BOLD response, LFPs, and single units (Logothetis et al., 2001). It was found that LFPs gave a better estimate of the BOLD response than the multi-unit activity. However, this is distinct from the study of large-scale correlated spontaneous fluctuations and it was uncertain whether spontaneous fMRI fluctuations would have the same electrophysiologic underpinnings.

Early attempts to study spontaneous activity in relation to fMRI were limited by the technical challenges in non-invasive methods. Goldman (2002) and Laufs (2003a) used simultaneous EEG/fMRI to investigate the spatial patterns of BOLD activity correlated to EEG power signals. However, the resultant fMRI correlation patterns had no specificity with spatial EEG source derivation (location of recording electrode) (Laufs, 2003b). This remained a major limitation of correlational analyses in MEG, where the point spread function is multiple centimeters and is further exacerbated by spatial leaking due to inverse model errors; in combination, this can lead to spurious correlations over long distance. Recent efforts to study RSNs with MEG have been more successful. Brookes et al. (2011) showed RSNs very closely matching BOLD in topography by investigating Hilbert envelope correlations using both seed-based (beta-specific) and temporal ICA methods. De Pasquale et al. (2009) showed that BLP fluctuations (equivalent to envelopes) are correlated within local fragments of networks, but analysis of short time windows produced more complete RSN topography. However, the MEG estimates of connectivity showed much higher levels of beta coherence compared to

electrophysiologic records, and also consistently fails to show gamma BLP correlation. This remains problematic for interpreting the frequency content of MEG studies, gamma BLP has been shown to be the best correlate of evoked BOLD responses to stimuli in invasive studies.

Concurrently with a decade of fMRI studies defining resting state networks (Lowe et al., 1998, Corbetta et al., 2000, Cordes et al., 2000, Greicius et al., 2003, Fox et al., 2005, Vincent et al., 2008) a growing body of literature in task-based electrocorticography (ECoG) experiments showed that invasive electrophysiology can effectively map functional systems including, for example, motor (Leuthardt et al., 2007), somatosensory (Bauer et al., 2006), auditory (Kaiser and Lutzenberger, 2005), memory (Sederberg et al., 2003), and language (Crone et al., 2001). Therefore ECoG was a very likely candidate method to measure correlations in the resting state corresponding to RSNs.

The current work was largely inspired by the successful attempts to measure large scale spontaneous correlations using ECoG(He et al., 2008, Nir et al., 2008). These studies established the large-scale correlation patterns of gamma BLP in humans, and spatial correspondence with fMRI has subsequently been confirmed by other groups (Keller et al., 2013). He et al. also established the existence of a correspondence between the phase of slow cortical potentials and fMRI correlations. This work raised many questions about the about the nature of spontaneous electrophysiologic fluctuations of brain activity. The demonstration of gamma BLP and SCP correlations within the motor network motivated a search for similar findings in other RSNs.

Given that frequency spectrum of LFPs and BLP modulations spans several orders of magnitude, these observations also raised of the question of whether similar findings were limited to SCP and gamma or extended to other frequencies. In chapter 5 we demonstrated that

SCP correspondence was a general property across RSNs. In the spectral domain, we found that LFPs exhibited correspondence to resting state fMRI correlations for frequencies extending up to the alpha range. Band-limited power fluctuations showed meaningful correlation patterns (i.e., similar to functional networks defined by fMRI) at multiple frequency ranges, specifically low frequencies (in the range of 4-30Hz) and gamma BLP. Surprisingly, LFP:fMRI correspondence did not show specific peaks for theta, alpha, beta, etc, and exhibited a nearly monotonic decrease in spatial correspondence with fMRI.

The presence of BLP correspondence in particular bands but only very low frequency LFP correspondence indicates that the amplitude modulation of brain rhythms is more coordinated at large spatial scales than the phase. These findings are consistent with the notion that power corresponds to the structure or activation of a functional system, whereas the phase encodes the information content (Itskov et al., 2008, Buzsaki, 2010, Buzsaki and Moser, 2013). It stands to reason that if the power and phase of brain activity generally demonstrated syncrony, then brain would constitute a system with catastrophically low information capacity.

Combined, the findings of Chapter 5-ECoG:fMRI correspondence across a range of frequencies and a range of cortical networks - inspired a search for spatio-spectral specificity in ECoG:fMRI correspondence. In other words, does the frequency of correlated spontaneous electrophysiologic fluctuations differ by RSN? In Chapter 6 we showed that the temporal frequencies previously associated with task-induced responses are specifically present in the correlation structure of spontaneous electrophysiological activity within the intrinsic and extrinsic functional systems.

There are several immediate extensions of this work. A modest amount of large-scale correlation was demonstrated in LFPs in Chapter 5 - it remains an open question whether there exists frequency specificity of these correlations. The lack of specific spectral features in LFP correlations suggests this is unlikely. However phase-amplitude analyses have demonstrated that theta-gamma coupling has been shown to be was strongest within the posterior precuneus cortex (PCC, a DMN component) whereas alpha-gamma coupling was strongest within primary visual cortex (an extrinsic system component) (Foster and Parvizi, 2012). These findings in combination with our results suggest that frequency of the phase signal is also likely to show specificity with respect to functional systems throughout the brain.

The most significant results of Chapter 6 are the details of the frequency specificity of BLP correlations in the theta to alpha range. Specifically, ECoG:fMRI correspondence in the alpha (8-12 Hz) and theta (4-8 Hz) bands was found within the extrinsic and intrinsic functional systems, respectively. These spectral associations are well documented in both task-based, non-invasive EEG (Klimesch, 1999, Pfurtscheller and Lopes da Silva, 1999) and invasive ECoG studies (Sederberg et al., 2003, Miller et al., 2007), but have not been reported in spontaneous activity. We show that these spectral features, which have been previously associated with specific cognitive domains, are topographically linked to RSNs known to instantiate extrinsic vs. intrinsic functionality. Therefore, we concluded that the frequencies of resting state correlations are likely to match those of task-based responses and that these frequencies are specific to functional systems.

In Chapter 7, we demonstrated that the spectral specificity of resting state correlations can be accounted for by the spectral content of behaviorally relevant fluctuations occurring at the same location. These results suggest that both task-related and spontaneous fluctuations are both governed by the regionally varying intrinsic oscillatory properties of the cortex. The data in this study allow for several future directions; all of the present data are based on contralateral arm movements, but similar analyses could be performed for the ipsilateral arm. We assume that the responses to contralateral movements represent a canonical activation of the motor network. However, given the prominence of symmetric interhemispheric correlations in resting state fluctuations, it is conceivable that as good or ever better correspondences could be found with those portions of the task response that are common to ipsilateral and contralateral responses.

It would also be possible investigate the features found in kinematics classification (or classification of different types of movements) and look for corresponding resting state correlation patterns. Such findings would demonstrates that spontaneous activity serves a function not just for broad functional networks, but also the subtler functional units within a system, or even information content. For example, it has been shown that fine functional structure can be observed in resting state electrophysiology, such as within tonotopic bands in the auditory cortex (Fukushima et al., 2012) and even orientation columns in visual cortex (Kenet et al., 2003).

The results in Chapter 7 are limited by the fact that both of the task paradigms induced responses in the alpha (and beta) / high-gamma complex within the extrinsic system. A combination of intrinsic and extrinsic system tasks in the same subjects would be desirable in future studies. One such task includes both components in the same paradigm: a task requiring subjects to either search for information in episodic memory vs. the environment demonstrated a

robust topographic separation of default mode network and dorsal attention regions in the parietal cortex, which is often covered by EGoG grids (Sestieri et al., 2010).

A correspondence between responses to intrinsic and extrinsic system tasks and resting state correlations within the same system at the same frequency implies an isomorphism between resting state and task activity. One functional interpretation of such a finding is that spontaneous activity constrains both the spatial topography and spectral organization of task-induced responses. Conversely, such results could also be interpreted as evidence that ongoing activity is a conglomeration of responses to the environment, spontaneous motor activity, and unconstrained cognition. Both of these interpretations may represent a futile attempt at establishing a cause and effect relationship between inseparable, or even tautological concepts. Indeed it has been shown that spontaneous activity affects future cognition (Sadaghiani et al., 2010, Baldassarre et al., 2012), but cognition affects future spontaneous activity (Lewis et al., 2009, Tambini et al., 2010). These perspectives can be reconciled by considering spontaneous activity not to be a separate, "offline" process distinct from "online" task-related activity, but rather the part of the fundamental machinery that the brain uses to instantiate function. Thus, the "resting state" is deceptively simply name for what is appears to be an unfettered, even overwhelming glimpse at the totality of the brain at work, as it perpetually seeks to interpret, respond to, and predict environmental demands (Raichle, 2010).

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