Characterization of mismatch between behavioral stimuli and FRMI data using the Kalman filter

Jason Steffener
New Jersey Institute of Technology

Follow this and additional works at: https://digitalcommons.njit.edu/dissertations

Part of the Biomedical Engineering and Bioengineering Commons

Recommended Citation
Steffener, Jason, "Characterization of mismatch between behavioral stimuli and FRMI data using the Kalman filter" (2005). Dissertations. 713.
https://digitalcommons.njit.edu/dissertations/713

This Dissertation is brought to you for free and open access by the Electronic Theses and Dissertations at Digital Commons @ NJIT. It has been accepted for inclusion in Dissertations by an authorized administrator of Digital Commons @ NJIT. For more information, please contact digitalcommons@njit.edu.
Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be “used for any purpose other than private study, scholarship, or research.” If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of “fair use” that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select “Pages from: first page # to: last page #” on the print dialog screen
The Van Houten library has removed some of the personal information and all signatures from the approval page and biographical sketches of theses and dissertations in order to protect the identity of NJIT graduates and faculty.
ABSTRACT

CHARACTERIZATION OF MISMATCH BETWEEN BEHAVIORAL STIMULI AND FMRI DATA USING THE KALMAN FILTER

by

Jason Steffener

The advance of blood oxygen level dependent function magnetic resonance imaging, (BOLD fMRI), allows researchers to non-invasively investigate the functioning human brain. The BOLD fMRI response to brief stimuli is called the hemodynamic response function (HRF), which can vary across brain regions and across subjects.

Models of the HRF are used to increase sensitivity of statistical maps; however, they often don’t account for spatial and temporal variance. Physiological effects, such as learning, fatigue or habituation, introduce mismatch between statistical models and the data. Methods that use minimal a priori information and track time varying signals are able to show the processing of information over time and thereby elucidate such effects.

The method of Kalman filtering was employed to characterize mismatches occurring between statistical models and BOLD data. The Kalman filter operates on data point by point. This contrasts regression techniques, that use blocks of data to find a single estimate.

Functional MRI data was collected from ten subjects at Columbia University while they engaged in three visual experiments and four olfactory experiments. The Kalman filter was used to distinguish between the fMRI response to a 2 second and a 12 second visual stimulus. The results from this analysis showed the extracted responses from the two stimuli significantly differed. The same analysis was also used to distinguish between primary and secondary olfactory cortices. These brain regions have shown differential temporal responses to odorants. The extracted responses were not significantly different.

Extracted responses from one stimulus (visual or olfactory) were used to test if this subject specific information would predict the next experimental session, better than standard a priori models of the data. The results of this analysis showed this not to be
the case. The extracted response over time to the odorant stimuli were tractable with the Kalman filter, and shown to decay as predicted from the literature. This temporal change was hypothesized to decrease predictability from one session to the next, causing the null result. To alleviate this, models were tested for their predictability across hemisphere, within session. The results showed that inclusion of subject specific information improved this fit over other \textit{a priori} models.

The implications of this analysis are the ability to extract temporally varying fMRI responses over an experiment without knowledge of the expected response to a stimuli. Results of such analyzes offer a look into how the brain responds and processes stimuli over the course of an experiment. This contrasts method that offer summary, or average, results from an experiment.
CHARACTERIZATION OF MISMATCH BETWEEN BEHAVIORAL STIMULI 
AND FMRI DATA USING THE KALMAN FILTER

by

Jason Steffener

A Dissertation
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Biomedical Engineering

Department of Biomedical Engineering

May 2005
CHARACTERIZATION OF MISMATCH BETWEEN BEHAVIORAL STIMULI AND FMRI DATA USING THE KALMAN FILTER

Jason Steffener

Dr. Stanley Reisman, Dissertation Advisor
Professor of Biomedical Engineering, New Jersey Institute of Technology

Dr. Ronald H. Rockland, Committee Member
Associate Professor of Biomedical Engineering, New Jersey Institute of Technology

Dr. Richard Foulds, Committee Member
Associate Professor of Biomedical Engineering, New Jersey Institute of Technology

Dr. Benjamin Martin Blau, Committee Member
Assistant Professor of Psychology, Rutgers University, Newark

Dr. Matthias Tabert, Committee Member
Assistant Professor of Clinical Psychiatry, Columbia University

Dr. Wen-Ching Liu, Committee Member
Assistant Professor of Radiology, University of Medicine and Dentistry of New Jersey
BIOGRAPHICAL SKETCH

Author: Jason Steffener
Degree: Doctor of Philosophy
Date: May 2005

Undergraduate and Graduate Education:

• Doctor of Philosophy in Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, 2005
• Master of Science in Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, 2000
• Bachelors of Science in Applied Physics, New Jersey Institute of Technology, Newark, NJ, 1997

Major: Biomedical Engineering

Presentations and Publications:


This work is dedicated to three important women.

My wife Florence for always making sure that I climb my mountains.

My mother Judith for showing me the value of hard work.

And Gudrun for taking a chance on me, even though my pants were too big and my hair was too long.
ACKNOWLEDGMENT

I wish to express my gratitude to my advisor, Dr. Stanley Reisman for always being there to offer support and guidance on this journey. It was his support that really made this pursuit possible.

I greatly appreciate all the support and feedback given to me by Dr. Matthias Tabert. He has spent large amounts of time with me discussing all aspects of the experiments to ensure their proper performance. I have benefitted so much from his guidance. I would like to extend my appreciation to Dr. Benjamin Martin Bly for his extensive support and valuable insight into my project. I also wish to thank Dr. Peter Bandettini for his insight and suggestions which have proven invaluable.

I would like to extend my gratitude to my committee for providing valuable feedback and guidance, Drs. Ronald H. Rockland, Richard Foulds and Wen-Ching Liu.

I also thank my Biomedical Engineering Department for supporting me through this academic endeavor and allowing me the opportunity to grow. It has been a challenging but fulfilling experience and I greatly value the opportunity I was given to teach. The Graduate Students Office has also been extremely supportive throughout my time at NJIT, and to them I owe appreciation, thank you Dr. Kane, Ms. Gonzalez and Ms. Randall.

I must also extend my gratitude to all the friends I have made during my time at NJIT, Anne Marie, Bruno, Diane, Don and Darnel. I have enjoyed all the time we spent together.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>ANATOMY AND PHYSIOLOGY</td>
<td>6</td>
</tr>
<tr>
<td>2.1 Magnetic Resonance</td>
<td>6</td>
</tr>
<tr>
<td>2.1.1 In the Perfect Magnetic Field</td>
<td>8</td>
</tr>
<tr>
<td>2.1.2 In the Non-Perfect Magnetic Field</td>
<td>11</td>
</tr>
<tr>
<td>2.2 Changing the Deoxy/OxyHemoglobin Ratio</td>
<td>14</td>
</tr>
<tr>
<td>2.2.1 Glutamate Recycling</td>
<td>14</td>
</tr>
<tr>
<td>2.2.2 Blood Flow Response</td>
<td>16</td>
</tr>
<tr>
<td>2.2.3 Blood Flow, Blood Volume, BOLD and the HRF</td>
<td>17</td>
</tr>
<tr>
<td>2.3 Anatomical Regions Involved in Olfaction</td>
<td>19</td>
</tr>
<tr>
<td>2.4 Shape of the Response</td>
<td>19</td>
</tr>
<tr>
<td>EXTRACTING THE HEMODYNAMIC RESPONSE FUNCTION</td>
<td>20</td>
</tr>
<tr>
<td>KALMAN FILTER THEORY</td>
<td>32</td>
</tr>
<tr>
<td>4.1 Theory</td>
<td>32</td>
</tr>
<tr>
<td>4.1.1 Summary of Kalman Filter Derivation</td>
<td>46</td>
</tr>
<tr>
<td>4.2 Implementation and Use of the Kalman Filter</td>
<td>47</td>
</tr>
<tr>
<td>4.2.1 Estimating the Variance Terms used in the Kalman Filter</td>
<td>47</td>
</tr>
<tr>
<td>4.2.2 Modifications for the Use with FMRI Data</td>
<td>52</td>
</tr>
<tr>
<td>SPECIFIC AIMS</td>
<td>56</td>
</tr>
<tr>
<td>5.1 Statement of Aims</td>
<td>56</td>
</tr>
<tr>
<td>5.2 Methods to Address Aims</td>
<td>58</td>
</tr>
<tr>
<td>5.2.1 Specific Aim 1</td>
<td>58</td>
</tr>
<tr>
<td>5.2.2 Specific Aim 2</td>
<td>60</td>
</tr>
<tr>
<td>5.2.3 Specific Aim 3</td>
<td>60</td>
</tr>
<tr>
<td>5.2.4 Specific Aim 4</td>
<td>64</td>
</tr>
</tbody>
</table>
# Table of Contents (Continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2.5 Specific Aim 5</td>
<td>65</td>
</tr>
<tr>
<td>5.2.6 Specific Aim 6</td>
<td>66</td>
</tr>
<tr>
<td>6 METHODS</td>
<td>67</td>
</tr>
<tr>
<td>6.1 Subjects</td>
<td>67</td>
</tr>
<tr>
<td>6.2 Experimental Setup</td>
<td>67</td>
</tr>
<tr>
<td>6.3 Paced Breathing Practice</td>
<td>68</td>
</tr>
<tr>
<td>6.4 Odor Detection Practice</td>
<td>70</td>
</tr>
<tr>
<td>6.5 Functional Scanning Setup</td>
<td>71</td>
</tr>
<tr>
<td>6.6 Olfactometer Construction</td>
<td>74</td>
</tr>
<tr>
<td>6.7 Odor Presentation Program</td>
<td>74</td>
</tr>
<tr>
<td>6.8 Post-scanning Odor Assessment</td>
<td>76</td>
</tr>
<tr>
<td>6.9 Visual Stimulus</td>
<td>77</td>
</tr>
<tr>
<td>6.10 Odorant Stimuli</td>
<td>77</td>
</tr>
<tr>
<td>6.11 Data Acquisition</td>
<td>78</td>
</tr>
<tr>
<td>6.12 Image Preprocessing Analyses</td>
<td>78</td>
</tr>
<tr>
<td>6.13 Region of Interest Mask</td>
<td>79</td>
</tr>
<tr>
<td>7 RESULTS</td>
<td>80</td>
</tr>
<tr>
<td>7.1 Behavioral Results</td>
<td>80</td>
</tr>
<tr>
<td>7.2 Visual Data</td>
<td>81</td>
</tr>
<tr>
<td>7.2.1 GLM Results from Sustained Stimulus</td>
<td>81</td>
</tr>
<tr>
<td>7.2.2 GLM Results from Transient Stimulus</td>
<td>83</td>
</tr>
<tr>
<td>7.2.3 Extracted Responses from Sustained and Transient Stimuli</td>
<td>85</td>
</tr>
<tr>
<td>7.3 Olfactory Data</td>
<td>89</td>
</tr>
<tr>
<td>7.3.1 GLM Results from Olfaction Data</td>
<td>89</td>
</tr>
<tr>
<td>7.3.2 Extracted Responses from Olfaction Data</td>
<td>91</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS
(Continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>Comparison of Kalman Filter Derived Model and other Statistical Models</td>
<td>95</td>
</tr>
<tr>
<td>7.4.1</td>
<td>Visual Data</td>
<td>96</td>
</tr>
<tr>
<td>7.4.2</td>
<td>Olfaction Data</td>
<td>98</td>
</tr>
<tr>
<td>7.4.3</td>
<td>Predicting the Opposite Hemisphere</td>
<td>100</td>
</tr>
<tr>
<td>7.4.4</td>
<td>Olfaction Data from Session One</td>
<td>100</td>
</tr>
<tr>
<td>7.4.5</td>
<td>Olfaction Data for Subsequent Sessions</td>
<td>105</td>
</tr>
<tr>
<td>7.5</td>
<td>Extraction of Time Dependent Changes</td>
<td>107</td>
</tr>
<tr>
<td>7.5.1</td>
<td>Inclusion of Estimated Decay Terms into Model Comparisons</td>
<td>113</td>
</tr>
<tr>
<td>7.6</td>
<td>Dependence of the Kalman Filter on its Training Data</td>
<td>119</td>
</tr>
<tr>
<td>7.6.1</td>
<td>Visual Data</td>
<td>119</td>
</tr>
<tr>
<td>7.6.2</td>
<td>Olfactory Data</td>
<td>122</td>
</tr>
<tr>
<td>7.7</td>
<td>Prediction Error across Time</td>
<td>124</td>
</tr>
<tr>
<td>8</td>
<td>DISCUSSION</td>
<td>125</td>
</tr>
<tr>
<td>8.1</td>
<td>Visual Data</td>
<td>125</td>
</tr>
<tr>
<td>8.2</td>
<td>Olfaction Data</td>
<td>126</td>
</tr>
<tr>
<td>8.3</td>
<td>Comparison of Statistical Models</td>
<td>132</td>
</tr>
<tr>
<td>8.3.1</td>
<td>Visual Data</td>
<td>132</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Olfaction Data</td>
<td>133</td>
</tr>
<tr>
<td>8.3.3</td>
<td>Cross Hemisphere Prediction</td>
<td>134</td>
</tr>
<tr>
<td>8.3.4</td>
<td>Tracking Time Dependent Changes</td>
<td>135</td>
</tr>
<tr>
<td>8.3.5</td>
<td>Exponential Information and the Kalman Filter Model</td>
<td>135</td>
</tr>
<tr>
<td>8.4</td>
<td>Training Data Dependence</td>
<td>137</td>
</tr>
<tr>
<td>8.5</td>
<td>Prediction Error across Time</td>
<td>137</td>
</tr>
<tr>
<td>8.6</td>
<td>Paced Breathing</td>
<td>138</td>
</tr>
<tr>
<td>8.7</td>
<td>Stimulus Presentation Programs</td>
<td>139</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

(Continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 CONCLUSION</td>
<td>140</td>
</tr>
<tr>
<td>APPENDIX A LINEAR ALGEBRA</td>
<td>142</td>
</tr>
<tr>
<td>APPENDIX B EXTRA RESULTS</td>
<td>143</td>
</tr>
<tr>
<td>B.1 Olfaction Data from Session Two</td>
<td>143</td>
</tr>
<tr>
<td>B.1.1 Left to Predict Right Hemisphere in Session Two</td>
<td>143</td>
</tr>
<tr>
<td>B.1.2 Right to Predict Left Hemisphere in Session Two</td>
<td>145</td>
</tr>
<tr>
<td>B.2 Olfaction Data from Session Three</td>
<td>147</td>
</tr>
<tr>
<td>B.2.1 Left to Predict Right Hemisphere in Session Three</td>
<td>147</td>
</tr>
<tr>
<td>B.2.2 Right to Predict Left Hemisphere in Session Three</td>
<td>148</td>
</tr>
<tr>
<td>B.3 Olfaction Data from Session Four</td>
<td>149</td>
</tr>
<tr>
<td>B.3.1 Left to Predict Right Hemisphere in Session Four</td>
<td>149</td>
</tr>
<tr>
<td>B.3.2 Right to Predict Left Hemisphere in Session Four</td>
<td>150</td>
</tr>
<tr>
<td>B.4 Estimated Decay and Model Comparison</td>
<td>151</td>
</tr>
<tr>
<td>B.4.1 Left to Predict Right Hemisphere</td>
<td>151</td>
</tr>
<tr>
<td>B.4.2 Right to Predict Left Hemisphere</td>
<td>154</td>
</tr>
<tr>
<td>APPENDIX C REGION OF INTEREST MASKS</td>
<td>157</td>
</tr>
<tr>
<td>APPENDIX D PROGRAMS USED IN THIS EXPERIMENT</td>
<td>164</td>
</tr>
<tr>
<td>D.1 MatLab Program to Perform Kalman Filter Analysis</td>
<td>166</td>
</tr>
<tr>
<td>D.2 MatLab Program of Kalman Filter Algorithm</td>
<td>171</td>
</tr>
<tr>
<td>D.3 MatLab Program for State Variable Variance Estimate</td>
<td>171</td>
</tr>
<tr>
<td>D.4 MatLab Program for Measurement Variance Estimate</td>
<td>172</td>
</tr>
<tr>
<td>D.5 MatLab program for Fitting an Exponential Curve</td>
<td>172</td>
</tr>
<tr>
<td>D.6 MatLab Program to Perform Analysis of Variance</td>
<td>173</td>
</tr>
<tr>
<td>D.7 MatLab Program to Perform Post-Hoc Analyses for Main Effect of Method</td>
<td>182</td>
</tr>
<tr>
<td>Chapter</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>D.8 MatLab Program to Perform Post-Hoc Analyses for Main Effect of ROI</td>
<td>183</td>
</tr>
<tr>
<td>D.9 LabView Program to Assess Paced Breathing</td>
<td>185</td>
</tr>
<tr>
<td>D.10 LabView Program to Control Olfactometer</td>
<td>187</td>
</tr>
<tr>
<td>D.11 LabView Program for Post-Scanning Assessment of Odorants</td>
<td>191</td>
</tr>
<tr>
<td>D.12 LabView Program used to Deliver Visual Stimuli</td>
<td>196</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>198</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Percent Variance Accounted for of Different Models</td>
<td>31</td>
</tr>
<tr>
<td>7.1 ROI Results for Sustained Visual Stimulus</td>
<td>82</td>
</tr>
<tr>
<td>7.2 ROI Results for Transient Visual Stimulus</td>
<td>84</td>
</tr>
<tr>
<td>7.3 Estimated Widths of Responses to Visual Data</td>
<td>88</td>
</tr>
<tr>
<td>7.4 ROI Analyses for Olfactory Stimuli</td>
<td>90</td>
</tr>
<tr>
<td>7.5 Estimated Widths of the Responses to the Olfaction Data</td>
<td>94</td>
</tr>
<tr>
<td>7.6 ANOVA Results for Visual Data from Sustained Stimulus</td>
<td>96</td>
</tr>
<tr>
<td>7.7 ANOVA Results from One Run of Data Tested the Second</td>
<td>98</td>
</tr>
<tr>
<td>7.8 ANOVA Results for Olfaction Data, Session One, Left Hemisphere Predicting Right</td>
<td>100</td>
</tr>
<tr>
<td>7.9 ANOVA Results for Olfaction Data, Session One, Right Hemisphere Predicting Left</td>
<td>103</td>
</tr>
<tr>
<td>7.10 ANOVA Results for Exponential Habituation Rate</td>
<td>107</td>
</tr>
<tr>
<td>7.11 ANOVA Results for Olfaction Data, Session One, Left Hemisphere Predicting Right, Including Decay</td>
<td>113</td>
</tr>
<tr>
<td>7.12 ANOVA Results for Olfaction Data, Session One, Right Hemisphere Predicting Left, Including Decay</td>
<td>116</td>
</tr>
<tr>
<td>7.13 ANOVA Table Within Visual ROI (BA 17)</td>
<td>120</td>
</tr>
<tr>
<td>7.14 ANOVA Table Within Olfactory ROI (Piriform Cortex)</td>
<td>122</td>
</tr>
<tr>
<td>8.1 Percentage and Actual Size of ROIs Scanned in All Subjects</td>
<td>131</td>
</tr>
<tr>
<td>B.1 ANOVA for Olfaction Data, Session Two, Left Hemisphere Predicting Right</td>
<td>143</td>
</tr>
<tr>
<td>B.2 ANOVA for Olfaction Data, Session Two, Right Hemisphere Predicting Left</td>
<td>145</td>
</tr>
<tr>
<td>B.3 ANOVA for Olfaction Data, Session Three, Left Hemisphere Predicting Right</td>
<td>147</td>
</tr>
<tr>
<td>B.4 ANOVA for Olfaction Data, Session Three, Right Hemisphere Predicting Left</td>
<td>148</td>
</tr>
<tr>
<td>B.5 ANOVA for Olfaction Data, Session Three, Left Hemisphere Predicting Right</td>
<td>149</td>
</tr>
<tr>
<td>B.6 ANOVA for Olfaction Data, Session Four, Right Hemisphere Predicting Left</td>
<td>150</td>
</tr>
</tbody>
</table>
LIST OF TABLES
(Continued)

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.7 ANOVA for Olfaction Data, Session Two, Left Hemisphere Predicting Right, Including Decay</td>
<td>151</td>
</tr>
<tr>
<td>B.8 ANOVA for Olfaction Data, Session Two, Right Hemisphere Predicting Left, Including Decay</td>
<td>154</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>A proton precessing about an external magnetic field. 8</td>
</tr>
<tr>
<td>2.2</td>
<td>Example T1 relaxation for multiple tissues. 10</td>
</tr>
<tr>
<td>2.3</td>
<td>Example T2 relaxation for multiple tissues. 11</td>
</tr>
<tr>
<td>2.4</td>
<td>Example images of three imaging modalities. 11</td>
</tr>
<tr>
<td>3.1</td>
<td>Explanation of Convolution 21</td>
</tr>
<tr>
<td>3.2</td>
<td>Example analysis with no HRF model 23</td>
</tr>
<tr>
<td>3.3</td>
<td>Example analysis with delay HRF model. 24</td>
</tr>
<tr>
<td>3.4</td>
<td>Example analysis with gamma model of HRF. 25</td>
</tr>
<tr>
<td>3.5</td>
<td>Example analysis with double gamma model HRF. 26</td>
</tr>
<tr>
<td>3.6</td>
<td>Example analysis with Kalman filter derived HRF. 27</td>
</tr>
<tr>
<td>3.7</td>
<td>The extracted HRF using the Kalman filter over the experimental time course. 28</td>
</tr>
<tr>
<td>3.8</td>
<td>Example analysis with shortened “on” period and the two gamma functions HRF. 29</td>
</tr>
<tr>
<td>3.9</td>
<td>Example analysis a decaying exponential model and a basis function set. 30</td>
</tr>
<tr>
<td>4.1</td>
<td>Hypothetical response to a twelve second stimulus used to determine filter order. Circles represent when a scan is acquired. 54</td>
</tr>
<tr>
<td>5.1</td>
<td>The seven designs compared for variance accountability 61</td>
</tr>
<tr>
<td>6.1</td>
<td>Synchronization of breathing and odor presentation for a rate of 10 breaths per minute. 68</td>
</tr>
<tr>
<td>6.2</td>
<td>Synchronization of breathing and odor presentation for a rate of 12 breaths per minute. 69</td>
</tr>
<tr>
<td>6.3</td>
<td>Picture showing a subject in the MRI and the manifold containing the odors. 72</td>
</tr>
<tr>
<td>6.4</td>
<td>Drawing of the MR room showing the subject setup. 73</td>
</tr>
<tr>
<td>7.1</td>
<td>Sustained visual stimulus GLM results. 81</td>
</tr>
<tr>
<td>7.2</td>
<td>Transient visual stimulus GLM results. 83</td>
</tr>
<tr>
<td>7.3</td>
<td>Extracted HRFs from sustained and transient visual stimuli. 85</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

## CONTINUED

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.4</td>
<td>Extracted HRFs from sustained and transient visual stimuli, continued.</td>
<td>86</td>
</tr>
<tr>
<td>7.5</td>
<td>Mean of the estimated widths of the responses as shown in Figures 7.4. Values determined as the full width at half the maximum value shown along with the standard error of the mean.</td>
<td>87</td>
</tr>
<tr>
<td>7.6</td>
<td>Results for olfaction group data in axial orientation overlaid on the group mean of all anatomical images.</td>
<td>89</td>
</tr>
<tr>
<td>7.7</td>
<td>Results for olfaction group data in coronal orientation overlaid on the group mean of all anatomical images.</td>
<td>90</td>
</tr>
<tr>
<td>7.8</td>
<td>Extracted HRF's in response to odorant stimuli.</td>
<td>91</td>
</tr>
<tr>
<td>7.9</td>
<td>Extracted HRF's in response to odorant stimuli.</td>
<td>92</td>
</tr>
<tr>
<td>7.10</td>
<td>Mean of the estimated widths of the responses as shown in Figures 7.8 and 7.9. Values determined as the full width at half the maximum value shown along with the standard error of the mean.</td>
<td>93</td>
</tr>
<tr>
<td>7.11</td>
<td>The seven designs compared for variance accountability</td>
<td>95</td>
</tr>
<tr>
<td>7.12</td>
<td>Main Effect of METHOD after first run of visual data and tested on the second run.</td>
<td>96</td>
</tr>
<tr>
<td>7.13</td>
<td>Main Effect of ROI after first run of visual data and tested on the second run.</td>
<td>97</td>
</tr>
<tr>
<td>7.14</td>
<td>Main Effect of ROI after first run of visual data and tested on the second run.</td>
<td>97</td>
</tr>
<tr>
<td>7.15</td>
<td>Non-significant main effect of METHOD after one session of training, and tested on the second session.</td>
<td>99</td>
</tr>
<tr>
<td>7.16</td>
<td>Main Effect of ROI after one session of training, and tested on the second session.</td>
<td>99</td>
</tr>
<tr>
<td>7.17</td>
<td>Main Effect of ROI after one run of training, and tested on the second run.</td>
<td>99</td>
</tr>
<tr>
<td>7.18</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session one.</td>
<td>101</td>
</tr>
<tr>
<td>7.19</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one.</td>
<td>102</td>
</tr>
<tr>
<td>7.20</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one.</td>
<td>102</td>
</tr>
<tr>
<td>7.21</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session one.</td>
<td>103</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>7.22</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one.</td>
<td></td>
</tr>
<tr>
<td>7.23</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one.</td>
<td></td>
</tr>
<tr>
<td>7.24</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session two.</td>
<td></td>
</tr>
<tr>
<td>7.25</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session two.</td>
<td></td>
</tr>
<tr>
<td>7.26</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session three.</td>
<td></td>
</tr>
<tr>
<td>7.27</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session three.</td>
<td></td>
</tr>
<tr>
<td>7.28</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session four.</td>
<td></td>
</tr>
<tr>
<td>7.29</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session four.</td>
<td></td>
</tr>
<tr>
<td>7.30</td>
<td>Main effect of ROI for exponential habituation rate.</td>
<td></td>
</tr>
<tr>
<td>7.31</td>
<td>Main effect of ROI for exponential habituation rate.</td>
<td></td>
</tr>
<tr>
<td>7.32</td>
<td>Time plot of data from the left olfactory ROI, the Kalman estimate of the data and the exponential fit to the peaks of each odor response.</td>
<td></td>
</tr>
<tr>
<td>7.33</td>
<td>Time plot of data from the left olfactory ROI and the Kalman estimate split over the four sessions of data. A: session 1, B: session 2, C: session 3 and D: session 4.</td>
<td></td>
</tr>
<tr>
<td>7.34</td>
<td>Time plot of data from the left olfactory ROI, the Kalman estimate of the data and the exponential fit to the peaks of each odor response.</td>
<td></td>
</tr>
<tr>
<td>7.35</td>
<td>Time plot of data from the right olfactory ROI and the Kalman estimate split over the four sessions of data. A: session 1, B: session 2, C: session 3 and D: session 4.</td>
<td></td>
</tr>
<tr>
<td>7.36</td>
<td>Surface graph of extracted response over time in left olfactory ROI.</td>
<td></td>
</tr>
<tr>
<td>7.37</td>
<td>Surface graph of extracted response over time in right olfactory ROI.</td>
<td></td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>7.38</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session one, including the decay model.</td>
<td>114</td>
</tr>
<tr>
<td>7.39</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one, including the decay model.</td>
<td>114</td>
</tr>
<tr>
<td>7.40</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one, including the decay model.</td>
<td>114</td>
</tr>
<tr>
<td>7.41</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.</td>
<td>115</td>
</tr>
<tr>
<td>7.42</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.</td>
<td>115</td>
</tr>
<tr>
<td>7.43</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.</td>
<td>115</td>
</tr>
<tr>
<td>7.44</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.</td>
<td>115</td>
</tr>
<tr>
<td>7.45</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>117</td>
</tr>
<tr>
<td>7.46</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one, including the decay model.</td>
<td>117</td>
</tr>
<tr>
<td>7.47</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one, including the decay model.</td>
<td>117</td>
</tr>
<tr>
<td>7.48</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>118</td>
</tr>
<tr>
<td>7.49</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>118</td>
</tr>
<tr>
<td>7.50</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>118</td>
</tr>
<tr>
<td>7.51</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>118</td>
</tr>
<tr>
<td>7.52</td>
<td>Mean and standard errors within the Visual ROI (BA 17) collapsed across test data for olfactory and visual training data.</td>
<td>120</td>
</tr>
<tr>
<td>7.53</td>
<td>Mean and standard errors within the Visual ROI (BA 17) collapsed across training data for olfactory and visual test data.</td>
<td>120</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES
(Continued)

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.54</td>
<td>Mean and standard errors within the Visual ROI (BA 17) for training/test combinations.</td>
<td>121</td>
</tr>
<tr>
<td>7.55</td>
<td>Example designs created from training on the first data set to be tested against the second data set within the visual ROI (BA 17).</td>
<td>121</td>
</tr>
<tr>
<td>7.56</td>
<td>Mean and standard errors within the olfactory ROI for the main effect of Training Hemisphere.</td>
<td>122</td>
</tr>
<tr>
<td>7.57</td>
<td>Mean and standard errors within the Olfactory ROI for training/test combinations.</td>
<td>123</td>
</tr>
<tr>
<td>7.58</td>
<td>Example designs created from training on the first data set to be tested against the second data set within the olfactory ROI (piriform cortex).</td>
<td>123</td>
</tr>
<tr>
<td>7.59</td>
<td>Estimate of extracted response at four time points from the right piriform ROI for the group mean and standard errors. The time points are: A 60, B 120, C 180 and D 240 seconds from the start of the experiment.</td>
<td>124</td>
</tr>
<tr>
<td>7.60</td>
<td>Estimate of extracted response at four time points from the left olfactory ROI for the group mean and standard errors. The time points are: A 60, B 120, C 180 and D 240 seconds from the start of the experiment.</td>
<td>124</td>
</tr>
<tr>
<td>8.1</td>
<td>Model of the HRF using half-cosines.</td>
<td>127</td>
</tr>
<tr>
<td>8.2</td>
<td>Half-cosine basis set.</td>
<td>128</td>
</tr>
<tr>
<td>8.3</td>
<td>Overlay of the two ROIs most affected by signal drop out and all voxels included in this analysis.</td>
<td>131</td>
</tr>
<tr>
<td>B.1</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session two.</td>
<td>144</td>
</tr>
<tr>
<td>B.2</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two.</td>
<td>144</td>
</tr>
<tr>
<td>B.3</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two.</td>
<td>144</td>
</tr>
<tr>
<td>B.4</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session two.</td>
<td>145</td>
</tr>
<tr>
<td>B.5</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two.</td>
<td>146</td>
</tr>
<tr>
<td>B.6</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two.</td>
<td>146</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>B.7</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session three.</td>
<td>147</td>
</tr>
<tr>
<td>B.8</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session three.</td>
<td>148</td>
</tr>
<tr>
<td>B.9</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session four.</td>
<td>149</td>
</tr>
<tr>
<td>B.10</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session four.</td>
<td>150</td>
</tr>
<tr>
<td>B.11</td>
<td>Significant main effect of METHOD trained on the left hemisphere to predict the right in session two, including the decay model.</td>
<td>151</td>
</tr>
<tr>
<td>B.12</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two, including the decay model.</td>
<td>152</td>
</tr>
<tr>
<td>B.13</td>
<td>Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two, including the decay model.</td>
<td>152</td>
</tr>
<tr>
<td>B.14</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.</td>
<td>152</td>
</tr>
<tr>
<td>B.15</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.</td>
<td>152</td>
</tr>
<tr>
<td>B.16</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.</td>
<td>153</td>
</tr>
<tr>
<td>B.17</td>
<td>Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.</td>
<td>153</td>
</tr>
<tr>
<td>B.18</td>
<td>Significant main effect of METHOD trained on the right hemisphere to predict the left in session one, including the decay model.</td>
<td>154</td>
</tr>
<tr>
<td>B.19</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two, including the decay model.</td>
<td>155</td>
</tr>
<tr>
<td>B.20</td>
<td>Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two, including the decay model.</td>
<td>155</td>
</tr>
<tr>
<td>B.21</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.</td>
<td>155</td>
</tr>
<tr>
<td>B.22</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.</td>
<td>155</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>B.23</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>to predict the left in session two, including the decay model.</td>
<td></td>
</tr>
<tr>
<td>B.24</td>
<td>Significant interaction of METHOD and ROI trained on the right hemisphere</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>to predict the left in session two, including the decay model.</td>
<td></td>
</tr>
<tr>
<td>C.1</td>
<td>Amygdala region of interest.</td>
<td>157</td>
</tr>
<tr>
<td>C.2</td>
<td>Anterior cingulate region of interest.</td>
<td>157</td>
</tr>
<tr>
<td>C.3</td>
<td>Brodmann Area 17 region of interest.</td>
<td>158</td>
</tr>
<tr>
<td>C.4</td>
<td>Brodmann area 18 region of interest.</td>
<td>158</td>
</tr>
<tr>
<td>C.5</td>
<td>Calcarine fissure region of interest.</td>
<td>158</td>
</tr>
<tr>
<td>C.6</td>
<td>Entorhinal region of interest.</td>
<td>159</td>
</tr>
<tr>
<td>C.7</td>
<td>Inferior frontal orbit region of interest.</td>
<td>159</td>
</tr>
<tr>
<td>C.8</td>
<td>Middle frontal orbit region of interest.</td>
<td>159</td>
</tr>
<tr>
<td>C.9</td>
<td>Superior frontal orbit region of interest.</td>
<td>160</td>
</tr>
<tr>
<td>C.10</td>
<td>Fusiform region of interest.</td>
<td>160</td>
</tr>
<tr>
<td>C.11</td>
<td>Hippocampus region of interest.</td>
<td>160</td>
</tr>
<tr>
<td>C.12</td>
<td>Insula region of interest.</td>
<td>161</td>
</tr>
<tr>
<td>C.13</td>
<td>Middle cingulate region of interest.</td>
<td>161</td>
</tr>
<tr>
<td>C.14</td>
<td>Olfactory cortex region of interest.</td>
<td>161</td>
</tr>
<tr>
<td>C.15</td>
<td>The union of orbital frontal and Brodmann area 47 region of interest.</td>
<td>162</td>
</tr>
<tr>
<td>C.16</td>
<td>Parahippocampal region of interest.</td>
<td>162</td>
</tr>
<tr>
<td>C.17</td>
<td>Piriform region of interest.</td>
<td>162</td>
</tr>
<tr>
<td>C.18</td>
<td>Posterior cingulate region of interest.</td>
<td>163</td>
</tr>
<tr>
<td>C.19</td>
<td>Superior temporal pole region of interest.</td>
<td>163</td>
</tr>
<tr>
<td>C.20</td>
<td>Thalamus region of interest.</td>
<td>163</td>
</tr>
<tr>
<td>D.1</td>
<td>LabView front panel of the program used to familiarize subjects with paced</td>
<td>185</td>
</tr>
<tr>
<td></td>
<td>breathing.</td>
<td></td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>D.2</td>
<td>LabView front panel of the program used to familiarize subjects with paced breathing.</td>
<td>185</td>
</tr>
<tr>
<td>D.3</td>
<td>LabView wiring diagram of the program used to familiarize subjects with paced breathing.</td>
<td>186</td>
</tr>
<tr>
<td>D.4</td>
<td>LabView front panel of the main odorant presentation program used during scanning.</td>
<td>187</td>
</tr>
<tr>
<td>D.5</td>
<td>LabView wiring diagram of the main odorant presentation program used during scanning.</td>
<td>188</td>
</tr>
<tr>
<td>D.6</td>
<td>First frame of the sequence in the main odorant presentation program.</td>
<td>189</td>
</tr>
<tr>
<td>D.7</td>
<td>Second frame of the sequence in the main odorant presentation program.</td>
<td>189</td>
</tr>
<tr>
<td>D.8</td>
<td>Third frame of the sequence in the main odorant presentation program.</td>
<td>190</td>
</tr>
<tr>
<td>D.9</td>
<td>The frame of the sequence which saves all behavioral data to a text file at the completion of the experiment.</td>
<td>190</td>
</tr>
<tr>
<td>D.10</td>
<td>LabView front panel of the post-scanning odorant assessment program.</td>
<td>191</td>
</tr>
<tr>
<td>D.11</td>
<td>LabView wiring diagram of the post-scanning odorant assessment program.</td>
<td>192</td>
</tr>
<tr>
<td>D.12</td>
<td>LabView front panel of the sub program for recording of subject perceptions.</td>
<td>193</td>
</tr>
<tr>
<td>D.13</td>
<td>LabView front panel of the sub program of post-scanning odorant assessment program used to rate the pleasantness of the odorant.</td>
<td>193</td>
</tr>
<tr>
<td>D.14</td>
<td>LabView wiring diagram for recording of subject perceptions.</td>
<td>194</td>
</tr>
<tr>
<td>D.15</td>
<td>LabView wiring diagram for rating odorant pleasantness.</td>
<td>194</td>
</tr>
<tr>
<td>D.16</td>
<td>LabView front panel of the odorant intensity rating scale.</td>
<td>195</td>
</tr>
<tr>
<td>D.17</td>
<td>LabView front panel of the main odorant presentation program used during scanning.</td>
<td>196</td>
</tr>
<tr>
<td>D.18</td>
<td>LabView front panel of the main odorant presentation program used during scanning.</td>
<td>197</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

The performance of functional brain mapping on the neural processing of odorants has posed difficulties to the imaging community [1]. Task-related signal change in regions has shown unreliable results across experiments. This behavior could result from differences in experiments or habituating neuronal responses to repeated odorant stimulation [2]. In relation to our everyday life, this would occur when we smell a perfume when we first put it on, but then the scent quickly fades. Upon return from work however, the perfume is still detectable to one’s spouse. The perfume did not entirely dissipate, leaving the alternate explanation that we just no longer detect it.

The work by Wilson 1998, showed this behavior through the implantation of electrodes in rats in a cortical location which processes odorants, the piriform, and the main olfactory bulb in the nose [2]. This work demonstrated that the cortical neurons actually did decrease their firing after repeated stimulation with the same odorant. This is contrasted by lack of firing decrease to a sequence of different odorants.

In the context of functional magnetic resonance imaging (fMRI) this issue of habituation has been addressed [3][4][5]. These researchers either modeled the habituation [3][5] to the response or simply described it[4]. Other authors have tried to avoid the effect by employing sequences of different odorants [6].

The work presented in this experiment combines experimental manipulation to limit the effects of habituation, along with a relatively novel approach to the analysis of fMRI data, the Kalman filter [7][8][9]. The Kalman filter is an adaptive filtering technique that does not analyze data as a complete block, but on a time point by time point basis. This sort of analysis truly takes advantage of fMRI’s advancement over PET in terms of temporal resolution.
The application of the Kalman filter to fMRI data is relatively new [10][11][12]; therefore, some form of verification is required. The first part of this work, focuses on this. In terms of validating the method, instead of creating simulated data for testing, data was collected from each subject while they engaged in visual stimulation experiments. These experiments collected data that shows robust task related signal change in predictable brain regions. The two visual stimuli were a 12 second and a 2 second flashing checkerboard. This data provided a testing ground for the Kalman filter.

The two experimental manipulations elicited two forms of task related signal change, a wide response of at least 12 seconds and a narrow response of at least 2 seconds. The Kalman filter was applied to this data to extract the response. This response is the task related signal change to each stimulus block, where every experimental manipulation consisted of five stimulus blocks. The advantage of the Kalman filter is that this response is extracted for every experimental time point, thus providing results that track the underlying signal.

This approach to testing the method is preferred over simulation, for it accurately captures all the unaccountable physiological effects taking place in real data. Simulated data makes attempts at physiological effects, such as respiration, cardiac and 1/f noise [13], but it will never be as good as the real thing. Therefore, this experimental manipulation is thought of as a simulation of the expected results from the olfaction experiment. Through the analysis of this visual data it is determinable whether this method is appropriate for use with fMRI data.

The next step in this project was to analyze data from an olfaction experiment. From this data, the responses to the odorant stimulation were extracted to test whether they differ across regions involved in the processing of odorant stimuli. The advantage of the Kalman filter approach to this problem, is that it makes no assumptions on the expected results. The only information it requires is that "something" happened at certain points in time.
Differences in the width of the extracted responses provide evidence that within odorant presentation time habituation is occurring.

From the results of these analyses the presence of cross experimental habituation is investigated. The peak amplitude of the estimated response is modeled to locate regions exhibiting habituation [2, 3]. This analysis takes advantage of the Kalman filter's adaptive nature.

The operation of the Kalman filter is to make a prediction of the next data point by using all the data up to it. Once the new data point is available, the prediction is refined. This logic is used to test whether the results from one experimental session of visual or olfaction data will predict the next session of data better than standard statistical models [14][15][16][17]. The expectation was that using a subject's own information from one session will improve statistical analysis of the subsequent session, while engaged in the same experimental manipulation. The comparisons are made between the Kalman filter informed model, and six others, and evaluated based on the percentage of variance in the data they account for.

The Kalman filter is employed in this study through training on one session of data and then testing on a subsequent data set. The question arises as to how reliant is the filter on the training data. The filter's reliance on accurate training data was validated through cross modality comparison, between the visual data and the olfaction. This tested whether the filter predicted olfaction data better when trained on olfaction data or whether there was no reliance on the training data.

These points are addressed through the following chapters. Chapter 2 focuses on the physiology underlying the signal measured. This discusses the effects the external magnetic field has on the human body and what physiological effects take place to create a measurable fMRI signal. Through this discussion the concept of the hemodynamic response function (HRF) is presented, which is the measured response to neuronal activity. Chapter 3 focuses on how this HRF has been modeled in the literature. The importance
of this chapter is in its discussion of the different models that have been proposed to better understand the fMRI signal and to increase the sensitivity of statistical models. The models discussed in this chapter are the same models which are compared to the predictions generated by the Kalman filter analysis to the data.

Chapter 4 gives the complete derivation of the Kalman filter and its application to fMRI. This chapter is of interest because it addresses special topics that are unique to fMRI data and how to deal with them. Chapter 5 presents the six specific aims of this work and the methods employed to address them. Chapter 6 describes the methods of this experiment. This chapter describes the experimental setup for conducting an olfactory experiment in addition to the programs that were required for control of the olfactometer and the behavioral data collection. The concept of paced breathing for the olfactory experiment is presented here. The image preprocessing is also discussed along with the creation of the regions of interest, with results presented in Chapter 7. Chapter 8 is the discussion and the work is concluded in Chapter 9.

In addition to an appendix of extra results, there are three other appendices. The first, Appendix A is a list of linear algebra equations that were used in the derivation of the Kalman filter. The second, Appendix C includes images of each of the regions of interest. Finally, Appendix D includes the main MatLab and LabView programs used to perform this experiment.

1.1 Contributions of this Work

This project has made significant contributions to the field of brain imaging and in particular olfactory experiments. The application of the Kalman filter to the study of fMRI is relatively new, and has not previously been done in the manner performed here. The work done here deconvolved out the underlying response to a stimulus at every time point in an experiment. This ability to extract time varying signals from fMRI data allows researchers
a tool to address various physiological questions. The investigation of habituation over an experiment, as performed in this work, is one example, others would be learning or fatigue.

The comparisons of multiple statistical model for the study of olfaction helps to understand the underlying response to odorant stimuli. Olfactory fMRI data has shown difficulty in the past because of its habituating activity. The model comparisons show which methods work best at elucidating task related signal change. This is an important contribution to the field because it shows which statistical models are the most appropriate.

The careful design of the olfactory experiment in this work has produced task related signal change in all regions of interest. The odorant timings and number of odorants to present have varied over many previous experiments, producing various results. The robustness of the data in this experiment provide a working template of methods for the conduction of olfactory experiments.

The programs developed for the conduction of this experiment, namely the LabView programs, provide a valuable contribution to the study of olfaction at Columbia University. The programs allow the researchers there much more flexibility in performing psychometric testing with subjects in a reliable computerized fashion. The use of the “split” screen technique allow the experimenter to observe every response the subject makes while they perform their tasks either in the MRI or outside.

The use of paced breathing in olfaction is also a new contribution to the field. This is in contrast to paced sniffing which has been shown to elicit its own network of task related signal changes that overlap with those involved in olfaction. The timing of paced breathing allow accurate sampling of presented odors so that all odors are inhaled at the same time across odorants and subjects.
Magnetic resonance imaging (MRI) has been a major breakthrough in the medical field and is revolutionizing science. The technological advance was significant enough that the 2003 Nobel Prize in Physiology or Medicine was awarded to its inventors Paul C. Lauterbur and Peter Mansfield. This technology is the fusion of physics and physiology; therefore, to properly explain the mechanisms of MRI some background in both of these disciplines is necessary.

2.1 Magnetic Resonance

Magnetic resonance imaging relies on the effects that a strong magnetic field has on the atoms in a biological sample. Most atoms have an intrinsic spin about a randomly oriented axis. It is the interaction of this spin with external magnetic fields that allows magnetic resonance imaging to take place. Every atom that possesses this spin property can be investigated with MRI. However, the hydrogen atom has the advantage of being in extremely large quantities in biological tissues, such as water and fat, and has a high spin to magnetic field strength ratio. For these reasons the hydrogen atom is a main focus of functional MRI experiments [18].

When placed in a magnetic field, a proportion of the randomly oriented hydrogen atoms align their spins around the direction of the field. The rate of this spin is called the Larmor frequency, calculated as:

$$\omega_0 = \frac{\gamma B_0}{2\pi}$$  \hspace{1cm} (2.1)

where $\gamma$ is the gyromagnetic ratio and $B_0$ is the external magnetic field strength. The gyromagnetic ratio is an atom specific value which relates spin rate to field strength. For
hydrogen this value is \(42.5774 \text{ MHz} T^{-1}\); therefore, at a field strength of 1.5 Tesla (as used in these experiments) the Larmor frequency of hydrogen is \(63.8646 \text{ MHz}\).

The number of hydrogen atoms that do align with the magnetic field, do not all align in the same direction. Some atoms align parallel, in a low energy state, and a smaller number align anti-parallel, in a high energy state; this split is called the Zeeman interaction. The ratio of atoms in the two orientations is known follows the Boltzmann distribution:

\[
\frac{N_{\text{upper}}}{N_{\text{lower}}} = e^{-\Delta E/kT}.
\]  

The \(N\) values are the number of atoms in the respective energy levels, \(\Delta E\) is the difference in energy between the levels, \(k\) is Boltzmann’s constant, \(1.381 \times 10^{-23} \text{ J} \cdot \text{K}^{-1}\), and \(T\) is the temperature.

The difference in the energy levels \(\Delta E\) is a function of the external magnetic field:

\[
\Delta E = \frac{\hbar \gamma B_0}{2\pi},
\]

which at 1.5 Tesla equals \(6.735 \times 10^{-27} \text{ J}\), thereby making the Zeeman interaction also a function of magnetic field strength.

Up to this point there is a collection of hydrogen atoms spinning at a rate of 63.8646 MHz and oriented parallel to the external field and a smaller collection spinning at the same rate oriented antiparallel to the field. The result of this ratio is a net magnetization of the tissue, denoted \(M_0\), in the same direction as the external magnetic field. If the ratio of parallel to antiparallel alignment is one, the result is a complete cancelation of net tissue magnetization. An ideal case is all alignment being in a single direction. In a perfect external magnetic field with a completely homogeneous tissue, the entire biological sample would have a magnetization of \(M_0\).
2.1.1  In the Perfect Magnetic Field

While in the magnetic field, $B_0$, atoms align in its direction. In order for these atoms to radiate a signal, and create images, energy is applied to the system. The external energy is a pulse with a frequency tuned to the exact spin rate of the hydrogen atoms. This frequency is in the radiofrequency (rf) range; therefore, the pulse is referred to as an rf pulse.

The orientation of the rf pulse is perpendicular to the external field, and is referred to as the $B_1$ direction. This causes all hydrogen atoms aligned (and anti-aligned) with the field to tilt into this perpendicular direction. Furthermore, the atoms all become coherent and precess around the external magnetic field in phase with each other. The result is no tissue magnetization in the longitudinal direction and all tissue magnetization, $M_0$, in the transverse plane [19].

Figure 2.1 A proton precessing about an external magnetic field.

Upon receiving this energy, the hydrogen atoms either absorb the energy to switch from the low to high energy level, or are stimulated to release their extra energy and switch from the high to low energy level. Once the rf pulse is turned off, the atoms begin to relax, or release their acquired energy or absorb energy to return to their state before the rf pulse.
As the atoms release energy they return their orientation to the direction of the external field, as shown in Figure 2.1.

The return of tissue magnetization in the $B_0$ direction is called the T1 relaxation, and the time it takes for 63% of the energy to return is the T1 relaxation time. Likewise, in the $B_1$ direction the decay of tissue magnetization is called T2 relaxation and the time it takes for tissue magnetization to decay to 37% is the T2 relaxation time.

The return of tissue magnetization in the longitudinal direction is modeled as:

$$M_{\text{longitudinal}}(\tau) = M_0(1 - e^{-\tau/T1})$$

where $\tau$ is the time since the rf pulse, $T1$ is relaxation rate for the particular tissue and $M_0$ is the tissue magnetization before the rf pulse.

Tissue contrast seen in MR images is the result of different tissues having different T1 relaxation times, as seen in Figure 2.2, and is mainly due to the environment the hydrogen atoms are in. When the hydrogen atoms are part of free water [19] the molecules move in a very rapid and disorganized manner, such as in Cerebral Spinal Fluid (CSF). This allows the molecules to retain the energy from the rf pulse for a long period of time, on the order of seconds. When the hydrogen atoms are in a more structured environment, such as bound water [19], they release their energy more quickly, causing a rapid T1 relaxation of the tissue, such as in brain tissue and fat.

The decay of tissue magnetization in the transverse plane is modeled as:

$$M_{\text{trans}}(\tau) = M_{\text{trans max}}e^{-\tau/T2^*}$$

where $M_{\text{trans max}}$ is the maximum tissue magnetization in the transverse plane immediately after the rf pulse and $T2^*$ is the decay time for the particular tissue. This is exemplified in Figure 2.3. The presence of the * superscript is explained in Section 2.1.2.

Although the relaxation curves in Figures 2.2 and 2.3 are cartoons, their time axes are in the appropriate range. The reason that the T1 and the $T2^*$ relaxation rates do not interfere
Figure 2.2 Example T1 relaxation for multiple tissues.

with each other is their different time scales. The long T1 relaxation is taking place in the $T^2*$ images but it has a small effect, and $T^2*$ relaxation has completely occurred before an image sensitive to T1 is acquired.

Figure 2.4 shows examples that relate the difference between the three imaging modalities. Image A shows a T1 image. Recall from Figure 2.2 that white matter decays the fastest and cerebrospinal fluid the slowest. This is reflected in the image because the white matter is the lightest, it has released the most energy, and the cerebrospinal fluid is the darkest because it is still storing its energy. The opposite is true for the T2 image as shown in image B. Referring to Figure 2.3, cerebrospinal fluid decays the slowest and white matter the fastest. The result is that cerebrospinal fluid is brightest and white matter the darkest. Image C in Figure 2.4 shows a $T^2*$ image which has similar image intensity qualities as the T2 image. Note the reduced resolution of this image. The reduction in resolution is the compromise for the rapid collection of this image type.
2.1.2 In the Non-Perfect Magnetic Field

At first glance it appears that the tissue magnetization decay in the transverse plane and its recovery in the longitudinal plane would be closely linked, but this is only in the most perfect magnetic situations. In reality there are many factors that disrupt the magnetic field. The cumulation of these effects is reflected in Equation 2.5 by the * superscript.
Within a tissue sample of a single molecule where each molecule has no effect on its neighbors, all hydrogen atoms would absorb the rf pulse and then continue to precess in phase with each other. What actually happens is that each hydrogen proton acts like a tiny magnet which disturbs its neighbor's magnetic field. Since the rate of precession is a function of the magnetic field (see Equation 2.1) any disturbances will change the rate of spin of the proton in question. The result is, two atoms spinning at slightly different rates will quickly be out of phase with each other. When the atoms become out of phase, the tissue magnetization in the transverse plane decreases, resulting in greater T2 relaxation (or decay).

The effect of neighborhood disturbances is reflected in Figure 2.3 where tissues have greater $T2^*$ relaxation rates than fluids. Bulk fluids involve little structure because all the molecules are moving so rapidly. The result is that two molecules do not inhabit the same space for any length of time; therefore, the molecules do not disturb each other's magnetic fields. The contrasting situation is in a tissue where hydrogen atoms are locked into a lattice with fixed neighbors. This allows the different atoms to interact and disturb each other.

Another effect on the T2 relaxation rate is termed spin-spin relaxation. This is where the rf pulse is absorbed by a tissue but the energy does not all relax and leave the lattice. Atoms in the high energy state release this energy when subjected to the rf pulse and low energy atoms absorb the energy of the rf pulse. After the pulse they each return to their original state. The atoms returning to the high energy state absorb energy from the atoms that are releasing energy to return to the low energy state. The result is that all the energy applied to the tissue is not released, but stored in the tissue. This situation takes place where the atoms are locked in a tissue lattice.

One slightly controllable effect on the $T2^*$ is the external magnet field homogeneity. Since the Larmor frequency of the atom is dependent on the magnetic field strength, any inhomogeneities affect the atom's spin rate. To limit this, MRI manufacturers attempt to make the magnetic field as homogeneous as possible [19].
The most interesting effect on the $T2^*$ relaxation rate comes from the presence of materials with magnetic properties which disturb the local field. A close inspection of the hemoglobin molecule will show it existing in two states, one bound to oxygen atoms and one not bound. The presence of oxygen bonds change the shape of this molecule and also its magnetic properties. The deoxygenated form of hemoglobin is paramagnetic disrupting its local magnetic field, where the oxygenated version is diamagnetic and does not. The result is that the $T2^*$ decay rate increases in the presence of deoxyhemoglobin resulting in image intensity decrease. An increase in oxyhemoglobin, relative to deoxyhemoglobin has the opposite affect on $T2^*$ decay rate. This effect on $T2^*$ by hemoglobin is termed blood oxygen level dependent (BOLD) and is the fundamental image contrast mechanism used for fMRI [20]. This BOLD contrast is affected by the local ratio of oxyhemoglobin to deoxyhemoglobin. Summarized as:

\[
\text{Image Intensity} \approx \frac{\text{oxyhemoglobin}}{\text{deoxygenated hemoglobin}} \quad (2.6)
\]

This ratio is not the direct cause of image intensity changes. In a resting state of neuronal activity, there exist a ratio of oxygenated blood to deoxygenated blood. The oxygenated blood has minimal effect on the local magnetic field while the deoxygenated blood alters it. The result is an effective resting $T2^*$ rate of signal decay. As this ratio changes, with more deoxygenated blood displacing oxygenated blood, there is an increased effect on the local magnetic field. The result is that hydrogen atoms dephase more quickly with their neighbors causing an increased $T2^*$ signal decay rate and a decrease in image intensity. The question is how do the ratios of oxyhemoglobin and deoxyhemoglobin change? To understand this question fully, a review of basic activity at the neuronal level is needed.
2.2 Changing the Deoxy/OxyHemoglobin Ratio

This review starts with an action potential arriving in a presynaptic terminal and finishes with the subsequent blood flow response. The arrival of an action potential causes depolarization of the terminal, causing a cascade of events of which one is the opening of voltage sensitive calcium channels. The influxing calcium initiates the release of vesicular glutamate neurotransmitter into the presynaptic membrane. Once externalized, the neurotransmitters diffuse across the cleft to bind to postsynaptic receptors. Once bound to receptors, the postsynaptic channels open or close, causing either excitatory or inhibitory post-synaptic potentials.

After the action potential, there is a large supply of neurotransmitter in the synapse, that which did not bind to post-synaptic receptors and that which was released by the receptors. This collection of neurotransmitters needs to be removed from the synaptic cleft before the arrival of the next action potential, to prevent an over abundance of neurotransmitter in the synapse. The neurotransmitters have multiple options for leaving the synapse, re-uptake into the pre-synaptic neuron, diffusing away from the cleft, degradation via oxidizing biochemicals or being transported into the surrounding astrocytes via sodium ion coupled transport.

It is the transportation into surrounding astrocytes that is focused on. Of the numerous neurotransmitters used in the brain, the two most common are glutamate and GABA (gamma aminobutyric acid). Glutamate is used by excitatory neurons which make up about 85% of the neurons and GABA is used by inhibitory neurons which make up about 15% of neurons [21].

2.2.1 Glutamate Recycling

As glutamate is the dominant neurotransmitter in the brain its passage is focused on. Once in the synapse, glutamate is quickly transported into a surrounding astrocyte via sodium ion transport and activates metabotropic glutamate receptors (mGluRs) [22]. In the astrocyte, a
glutamate molecule is converted to glutamine using one molecule of ATP and one ammonia molecule through the enzymatic process of glutamine synthetase. This glutamine molecule then diffuses out of the astrocyte back into the neuron. In the neuron, glutamine is converted back to glutamate. The glutamate molecules are then transported back into vesicles via hydrogen transports. This transport allows one hydrogen atom out of the vesicle and one glutamate molecule in, where the hydrogen atoms are actively pumped in using ATP. The cycle is now complete with the glutamate molecules returned to their original location. The uptake of glutamate into surrounding astrocytes is the basis for an updated theory on the mechanism of functional hyperemia [22].

This entire process of neurotransmitter recycling requires approximately 70% of the total energy needs of the brain [21], where the major source is glucose [23]. Glucose is transported to the brain through the vascular system and is withdrawn from blood vessels by the astrocytes which are wrapped around them. Therefore, the astrocytes not only structurally support the vessels, but in current theories they actively withdraw nutrients from them [22][24][25].

Once in the astrocyte, a glucose molecule is broken down to two molecules of pyruvate via glycolosis. This process uses two molecules of ATP and creates four. From this net ATP production, one ATP is used for the glutamate to glutamine conversion and the other is for a sodium/potassium pump (sodium in and potassium out). The increased interior sodium concentration is from the sodium ion coupled transport of glutamate into the cells. From the astrocyte, the two pyruvate molecules diffuse into the neuron [26] and enter the Krebs cycle and the electron transport chain where 34 ATP molecules are made [27]. The neuronal ATP is subsequently used for the restoration of chemical gradients after the action potential arrival.
2.2.2 Blood Flow Response

Glutamate, and all neurotransmitter, recycling, is the brain's main energy sink, this accounts for approximately 85% of all energy usage [21]. Therefore, a large amount of glucose and oxygen is needed, in addition to the removal of metabolites. These two mechanisms are facilitated via the brain's vasculature. The relationship between cerebral neuronal activity, blood flow (CBF), blood volume (CBV) and metabolic rates (CMR) are the basis of neuroimaging and BOLD fMRI in particular.

The brain is never truly at rest; therefore neuroimaging focuses on the brain’s activity as it increases above resting levels in response to stimuli. Positron emission tomography (PET) has shown the ratio of cerebral metabolic rate (CMR) of oxygen to glucose is approximately 4.1 for the entire brain [28]. This value is based on the $CMR_{O_2}$ equalling $1.50 \pm 0.071 \text{(SD)} \mu mol/\text{(min\cdot 100g)}$ and the $CMR_{glu}$ equalling $0.37 \pm 0.053 \text{(SD)} \mu mol/\text{(min\cdot 100g)}$ for the entire brain. Therefore at resting levels the brain uses 4.1 times more oxygen than glucose. In an area like the visual cortex this ratio is preserved with $CMR_{O_2}$ equalling $1.71 \pm 0.183 \text{(SD)} \mu mol/\text{(min\cdot 100g)}$ and the $CMR_{glu}$ equalling $0.42 \pm 0.033 \text{ (SD)} \mu mol/\text{(min\cdot 100g)}$ [29]. This increased metabolic rate, but same ratio, shows brain regions that have increased blood flow rates also have increased metabolic rates [28]. This study showed that at rest there is a tight coupling between flow rates and metabolism.

This tight coupling between CBF and CMR breaks down on local increases in neuronal activity. In somatosensory regions, in response to a tactile vibratory stimulation, CBF increased by 29% and the $CMR_{O_2}$ increased 5% [28]. Similar results were found in visual cortex with CBF increasing 50% and the $CMR_{O_2}$ increasing 5%. In addition the $CMR_{glu}$ was shown to increase 51% [29]. The uncoupling of CBF and $CMR_{O_2}$ shows that the increased blood flow is not a response to increased need for oxygen. Because $CMR_{glu}$ increases without an equal increase in $CMR_{O_2}$ it is concluded that “91% of the activity-induced increase in glucose uptake was not oxidized [29].” Therefore the glucose must have been metabolized via glycolysis into lactate or stored in the astrocytes as glycogen.
via glycogenesis. This uncoupling of cerebral metabolic rates of oxygen and glucose show that increases in CBF due to increased neuronal activity is not in response to maintaining glucose oxidation levels.

The answer to what causes the increase in blood flow is broadly speculated. It may not even be a single event that causes it, but a conglomerate. One speculation, is the increased levels of potassium in the astrocytes, via the sodium/potassium pump [30] as a result of neuronal activation, may be used to trigger the blood vessels the astrocytes abut [29]. The lactate that builds up as a result of the anaerobic metabolism [29] of glucose during increased neuronal activity may be a trigger [31]. Another suggested trigger is nitric oxide [31].

These existing theories of neuronal activity induced vasodilation are under revision with current research into the role of astrocytes [22]. The theory proposed by Zonta et al. [22][24][25] states that increased neuronal activity causes release of the neurotransmitter glutamate into the synaptic cleft. The glutamate is taken up by surrounding astrocytes and activates metabotropic glutamate receptors thereby triggering calcium ion oscillations in the astrocyte and surrounding astrocytes. The calcium ion increases regulate the release of vasodilation agents. The measurable BOLD fMRI signal is affected by the vasodilation due to its direct relationship to the ratio of deoxyhemoglobin to oxyhemoglobin. This ratio as related to BOLD, CBF and CBV is now considered.

2.2.3 Flow, Volume, BOLD and the Hemodynamic Response Function

The ensemble of activity that results in a measurable BOLD fMRI signal is termed the hemodynamic response function (HRF). This is a function of time that describes the transitory behavior of the signal in response to a short increase in neuronal activity. This function has a delayed post-stimulus peak time on the order of 4 to 6 seconds followed by an undershoot below the baseline signal level.
To understand this resultant signal consider the resting brain to have resting levels of oxygenated blood and deoxygenated blood in the venous system. The arterial side of the capillary bed is not considered because it is always full with oxygen rich blood, which minimally interferes with the local magnetic field. When CBF increases, the oxygen extraction fraction decreases [28][29]. The result is that oxygen rich blood flows into the venous system displacing the existing oxygen poor blood. The ratio of oxyhemoglobin to deoxyhemoglobin thus changes from more deoxyhemoglobin to more oxyhemoglobin. Therefore, there is less magnetic field interference, and the hydrogen atoms stay in phase with each other longer, after the rf pulse. The result is an increase in BOLD fMRI signal change as a function of neuronal activity increase.

The above discussion focused on the cause of the increase in signal strength; however, a post-stimulus undershoot is also known to occur. As CBF increases the venous system is thought to behave like an expandable balloon thereby increasing the CBV and quickly filling with oxygen rich blood [32][33]. Once the increase in neuronal activity ceases, the CBF falls back to resting levels. The expanded blood vessels also shrink back to resting sizes at a slower rate. As the vessels shrink, this increased blood volume fills with deoxyhemoglobin, resulting in a local level greater than that before the increased neuronal activity. The result is a lingering decrease in signal after increased neuronal activity.

The signal measured in a blood oxygen level dependent functional magnetic resonance imaging experiment is hypothesized to relate to neuronal activity. This is the case however through a complicated interaction of physics and biology. The resultant signal is actually caused by the replacement of magnetic field interfering diamagnetic deoxyhemoglobin molecules with non-interfering paramagnetic oxyhemoglobin molecules. The delivery of the excess oxygen rich blood is caused by vasodilation resulting from astrocytic signals triggered by calcium ion waves. Glutamate release from action potentials in neurons, triggers astrocyte glutamate receptors thereby inducing the calcium waves.
2.3 Anatomical Regions Involved in Olfaction

The olfactory system can is thought to have a primary system and a secondary system. Once an odorant is received on the olfactory epithelium a signal is sent via the olfactory bulb into the brain [34]. The first synapses this signal makes is referred to collectively as the primary olfactory cortex. Royet and Plailly 2004 present a review of the literature and present the following anatomical locations as being involved in olfactory signal processing [35]. From the olfactory bulb the signal is sent to the anterior olfactory nucleus, the tenia tecta, the olfactory tubercle, the piriform cortex, the anterior cortical amygdaloid nucleus, the periamygala cortex and the entorhinal cortex. Collectively these regions are the primary olfactory cortex (POC) [36]. From the piriform and the olfactory tubercle a signal is projected to the thalamus and from the thalamus to the insula and orbital frontal cortex. The entorhinal cortex projects to the hippocampus and the piriform projects to the orbital frontal cortex and the insula. These regions are referred to collectively as the secondary olfactory cortex.

2.4 Shape of the Response

In developing their mathematical model of the HRF, Buxton et al. 1998 [32] describe the shape of the HRF as follows. There is an initial 2 to 3 second delay between the start of the stimulation and the inflexion point of the fMRI signal. The fMRI signal increases to peak around six to 10 seconds post stimulus and plateaus if the stimulation is sustained. Post stimulus there is a ramped decrease to undershoot the initial baseline value, after which it settles back to baseline. In the presence of a transient stimulus this ensemble of events takes at most 32 seconds.
A goal of functional brain imaging is to gain greater insight into how the brain processes information and responds to external stimuli. In order to facilitate this goal, in the context of functional magnetic resonance imaging (fMRI), an often used technique is that of statistical parametric mapping [14]. This technique is founded on linear regression; however, it also accounts for the multiple tests that are performed on adjacent points in the brain which are not entirely independent. In order to increase the sensitivity of such mapping techniques, research has probed the measured underlying signal. This is the signal response to an impulsive input, also termed the impulse response function, and in the context of fMRI is the hemodynamic impulse response function (HRF) [31]. Understanding the behavior of this signal improves statistical models and increases their sensitivity, which is important to understand what regions of the brain are involved in the performance of a task. This underlying signal has been modeled with a variety of techniques which all have some commonalities.

These commonalities include the use of an entire experimental block of data to estimate a single response (batch techniques) and the use of a response model from one brain region to model other or all other regions in the brain. An inherent limitation these methods have is due to their batch processing. Batch processing uses an entire time vector to create a single estimate. The result is a generalized estimate over the experimental time.

Use of an entire block of data for a single estimate ignores the variance of the signal over experimental time which may hold valuable clues to the brain’s responses over time. Using a general pre-specified model also assumes the response to a stimulus is the same across brain regions. While modeling the HRF is important, these limitations may hide important information. The proposed Kalman filter method is not constrained by these
Before discussing the Kalman filter in depth, a review of existing models is required. Models of the HRF are used to increase the sensitivity of statistical tests. This is done through the HRFs convolution with the stimulus model. Convolution uses a model of the HRF to modify the stimulus design, thereby accounting for effects the system has on the input, to create the system's output. Figure 3.1 shows the steps. The top left plot represents the input stimulus, the * represents the convolution operation, the top right plot shows a model of the HRF and the bottom plot is the convolution of the two. Convolution of the input stimulus with a model of the HRF allows for incorporation of the delay and temporal

**Figure 3.1** The top left panel shows a stimulus design vector, the top right shows a model of the underlying hemodynamic response function and the bottom plot shows the convolution of the two.

issues and is able to estimate the underlying stimulus response and track its evolution over the experimental time. It is also possible to extract the response to a stimulus in the region of interest.
spread that is imposed on the input stimulus. This operation is modeled with the equation:

\[ y[n] = (X * h) \cdot \beta + \nu_2 \]  \hspace{1cm} (3.1)

where \( X \) is the design, the top left plot, \( h \) is the model of the HRF, the top right plot, \( \beta \) is a scaling factor, and \( \nu_2 \) is additive noise. Deconvolution, the inverse of convolution, uses the data, \( y[n] \), and the design, \( X \), to estimate the HRF, \( h \), while regression uses the data, the design and the HRF to estimate the beta weight.

The next section will discuss different models of the HRF that have been used in the literature. Examples of each model will be given along with the results obtained when these models are used on an example of real data.

### 3.1 Models of the Hemodynamic Response Function and Regression

Models of the HRF have developed from pure delays, to Gamma variate functions, to the subtraction of Gamma variate functions and to basis functions. To exemplify each of a series of models, data is used from the Calarine fissure. This data is the average across all voxels in the left Calcarine fissure for a single 52 year old male subject. He was scanned at the Hatch Center for MR Research in the Neurological Institute at Columbia University using a 1.5 Tesla Philips Medical Systems Intera scanner (equipped with a SENSE head coil, TR/TE=3000/30ms, FOV=220x220mm, matrix 64x64, 32 slices at 4mm thick) while observing a flashing checkerboard visual stimulus. This stimulus was delivered from a lap-top computer and back-projected with an LCD projector onto a screen that the subject was able to see through a mirror mounted above his eyes. This stimulus alternated between flashing for twelve seconds and a fixation cross for thirty seconds, for five cycles. Each model is compared based on the percentage of variance the model accounts for in the data. This was calculated as the percentage of variance a model accounts for. As an equation this
Figure 3.2 The top left plot shows the stimulus design vector, the top right plot shows that no model is used to model the HRF, the bottom plot shows the raw data overlap with the model of the data.

\[
\text{Percent variance accounted for} = \left(1 - \frac{\text{var}(\text{residuals})}{\text{var}(\text{data})}\right) \times 100 \quad (3.2)
\]

After the discussion of each model, the resultant percent variance accounted for along with the corresponding statistical T values and probabilities are summarized in table 3.1.

The first noticed effect of the HRF on the output data was the delay imposed on the input stimulus [15]. Without taking this delay into account, the stimulus model accounts for only 12.6217 percent of the variance in the data when using Equation 3.2. Figure 3.2 shows the input model, with no model defined for the HRF. There is an obvious delay between the data and the model that is unaccounted for. Once a pure delay of 3 seconds is incorporated into the model, see Figure 3.3, the amount of variance accounted for increases to 25.1465 percent, again using Equation 3.2. Note how convolution with the pure delay, shifts the
Figure 3.3  The top left plot shows the stimulus design vector, the top right plot shows a pure delay of six seconds was used to model the HRF, the bottom plot shows the raw data overlap with the model of the data.

design in Figure 3.3 to the right relative to the no HRF model design in Figure 3.2. A better model of the HRF was made using a Gamma function [16]. This model accounts for a delay, and includes a smooth increase to a peak value and a smooth decrease to baseline after a stimulus event. This model now accounts for 37.3109 percent of the variance in the data and is shown in Figure 3.4. The design in this case is delayed relative to the no model case and has rounded edges. These edges are a result of the smooth model of the HRF. Following this, the undershoot of the HRF was modeled. This is when the HRF returns to baseline post-stimulus, and actually falls below baseline before increasing again and settling to zero [17]. Adding this new feature to the HRF model increase the variance accounted for to 38.3836 percent, see Figure 3.5.

Up to this point, all the proposed models can be thought of as fitting procedures that were developed after data collection. Once the data was investigated, the models were
Figure 3.4 The top left plot shows the stimulus design vector, the top right plot shows the Gamma variate function used to model the HRF, the bottom plot shows the raw data overlap with the model of the data.

designed based on what was seen in the data. For example, once the delay was observed, the model was adjusted to incorporate this information. These models are also not data, subject or even group specific. They were developed on groups of healthy young subjects in response to either visual or motor stimulation. Even with their development derived from a narrow focus, their application, in particular the difference of two gamma functions, shows they are apparently generalizable.

The derivation of such models from their respective stimulus modalities and subject populations assumes that the modeled HRF is the same across brain regions and subjects. This has been proven to not be the case [37]. As a solution, some authors use subject specific, but not stimulus modality specific, HRF models [38]. This solution accounts for differences in the HRF across subjects but not across brain regions.
Figure 3.5 The top left plot shows the stimulus design vector, the top right plot shows the difference of two Gamma functions used to model the HRF, the bottom plot shows the raw data overlap with the model of the data.

The Kalman filter, as implemented in this work, performs operations similar to deconvolution[17][39] for extracting the HRF, with the added feature that the deconvolved signal is now a function of time. The equation for the standard model:

$$y[n] = (X * h) \cdot \beta + \nu_2.$$

is changed to account for this function of time as:

$$y[n] = X * \tilde{h}[n] + \nu_2[n] \quad (3.4)$$

where the beta weight is not explicitly modeled and the signal’s progression though time is modeled as:

$$\tilde{h}[n + 1] = \tilde{h}[n] + \nu_1[n]. \quad (3.5)$$
Figure 3.6  Top left plot shows the stimulus design vector, top right shows the extracted HRF using the Kalman filter from the opposite hemisphere, bottom shows the raw data overlapped with the model of the data using the extracted HRF.

The HRF, $\tilde{h}[n]$, is now extracted at each time point, $n$, so the total size of this matrix is time points by order, where order corresponds to the number of time points of data collected during the length of the HRF.

With the extraction of the HRF as a function of time, it is investigated for any time varying behavior. Such variances could include a varying dispersion (width) of the response or a varying response strength. This information is unobtainable from techniques like deconvolution that extract a single estimate of the HRF. An example is shown in Figure 3.6. This figure shows the original stimulus design in the top left plot. The top right plot shows an estimate as extracted by the Kalman filter of the underlying response to the stimulus. To avoid circular analyses, the estimate of the underlying response is calculated from the data in the same subject, data set and region of interest, but in the opposite hemisphere. With the information gained from the right hemisphere, a model of the data in the left hemisphere is
created. After this model is estimated 51.3259 percent of the variance is accounted. The result is shown in the bottom plot of Figure 3.6.

The added benefit of the temporal tracking ability of the Kalman filter is evident in Figure 3.7. This “mountain range” plot shows the evolution of the extracted HRF over the experiment time course. Clearly evident, is the amplitude variation in the extracted response. Investigation into this transition across experimental time is not possible with deconvolution.

Two other models were also compared in this work to assess the levels of task related signal change in the olfactory data. Their derivation is based on discussions in the literature. The first is based on the results found in Poelinger et al. [4]. From this discussion, a stimulus design that only modeled the first six seconds of each stimulus presentation as being relevant, was convolved with the difference of two gamma functions. The result is a model that has an “on” period of six seconds instead of twelve seconds as shown.

**Figure 3.7** The extracted HRF using the Kalman filter over the experimental time course.
Figure 3.8  The top left plot shows the stimulus design vector with a six second “on” period, the top right plot shows the difference of two gamma functions used to model the HRF, the bottom plot shows the raw data overlap with the model of the data.  

This model accounted for 18.1965 percent of the data’s variance and the results are shown in Figure 3.8. Another method of estimating the underlying response to a stimulus is with a basis function set. This is a more flexible analysis approach than using a single statistical model and has shown promise in the literature [40][41][42]. Basis functions are a series of functions specifically designed to maximally span a space of interest. The set used is termed the constrained optimal linear basis set, see the original paper for a complete description [40]. In combination with this basis set of three functions, a priori knowledge is included about expected olfactory responses. Sobel et al. [3] proposed in their work a decaying exponential function to model the rapidly habituating within odorant presentation time response. Taken from the description and graphs in this paper, the seventh model used in this work, a decaying exponential model, was designed and combined with the three basis functions. The basis function and the exponential model are
Figure 3.9 The top left plot shows the exponentially decaying stimulus design vector as derived from the work by Sobel et al. [3], the top right plot shows the basis function set as described in Woolrich et al. [40], the bottom plot shows the raw data overlap with the model of the data.

shown in Figure 3.9. This model is intended for the olfactory data used in this experiment; therefore, it is not ideal for the application to the example visual data. The percent variance accounted for is 38.3836.

To summarize, seven models were compared. These are listed along with the amount of variance they accounted for in the example data in table 3.1. This initial demonstration of the models offers promise of the applicability of the Kalman filter method when compared to other models.

The use of linear regression and that of deconvolution are essential steps in understanding and interpreting fMRI data. The benefit of using the Kalman filter, is the investigation of temporal variability in the fMRI data across experimental time. Such variances need not be known a priori but can be estimated from the data; these effects include fatigue,
Table 3.1 Percent Variance Accounted for of Different Models

<table>
<thead>
<tr>
<th>Model of HRF</th>
<th>Percent Variance Accounted for</th>
<th>Statistical T value</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12.62</td>
<td>2.98</td>
<td>0.005</td>
</tr>
<tr>
<td>Pure Delay</td>
<td>25.15</td>
<td>4.46</td>
<td>4.98e-05</td>
</tr>
<tr>
<td>Single Gamma</td>
<td>37.31</td>
<td>5.58</td>
<td>6.67e-07</td>
</tr>
<tr>
<td>Difference of two Gammas</td>
<td>38.38</td>
<td>5.94</td>
<td>1.51e-07</td>
</tr>
<tr>
<td>Six second “on” period model</td>
<td>18.20</td>
<td>3.85</td>
<td>4.09e-04</td>
</tr>
<tr>
<td>Kalman Filter Extraction</td>
<td>51.33</td>
<td>8.50</td>
<td>2.03e-12</td>
</tr>
<tr>
<td>Decaying exponential and basis set</td>
<td>43.46</td>
<td>6.07</td>
<td>9.35e-08</td>
</tr>
</tbody>
</table>

learning or habituation. The following chapter goes through the derivations of the Kalman filter technique to allow its computer implementation, specifically for tracking fMRI data sets.

It is worth noting the origins of Kalman filter are in the field of RADAR tracking [7]. The technique is also widely used in financial tracking and prediction[43] [44], and is the foundation for neural network models [8]. The filter can give similar results to linear regression analyzes; however, it is adaptive and can change its estimates over experimental time. Being adaptive, the filter starts at the beginning of a data set and makes estimates to the underlying signal, these estimates are refined as the data “learns” more about the underlying signal from incoming data. Once the filter “learns” what the underlying signal is, it can effectively track it as it varies across time.

This tracking ability is of obvious importance in RADAR in order to predict where an object is and what its trajectory is. For financial data the method is similar just with different data. In the context of neural networks the filter uses training data to “learn” about the signal and then can make predictions from data of interest, post training.
CHAPTER 4
KALMAN FILTER THEORY

4.1 Theory

This section describes the theory behind the Kalman filter and its derivation. This section is based on the derivation of the Kalman Filter by Simon Haykin in his book "Adaptive Filter Theory", fourth edition, 2002 [9], with support from [8][45][46]. The filter is re-derived in a manner focusing on the nature and structure of the data used.

The technique relies on models of the data which will remain general and will not be specific to fMRI applications until a later section when the uses of this technique are discussed. First, a system model is needed. Assuming a linear system, upon inputting a signal to the system a resultant output ensues. This output is some unknown function of the input. In contrast to linear regression, which assumes a time fixed model, the Kalman filter allows this function to vary in time. This is a key important feature of the usefulness of the filter. Also with any measurement there will be noise. The measurement equation is now:

\[ y(t) = X(t) \ast h(t) + \nu_2(t) \]  \hspace{1cm} (4.1)

\( y(t) \) is the measured output of the system as a function of time, \( X(t) \) is the input to the system as a function of time, \( h(t) \) is the unknown behavior of the system which is allowed to vary over time and \( \nu_2(t) \) is the measurement noise.

In the context of linear regression, the \( h(t) \) term is not a function of time and is determined using the concepts of Wiener filtering. Wiener filtering determines the value of \( h \) that minimizes the mean square error between the measured data and the known input, \( X(t) \times h \). The key point here is the mean-square error is minimized.

In the context of Kalman filtering, the unknown function \( h(t) \) is a function of time and termed the state of the system. This state variable is represented with the process
equation:

\[ h(t + 1) = F(t + 1 | t)h(t) + \nu_1(t) \quad (4.2) \]

where \( F(t + 1 | t) \) describes the transition of the state variable from time point \( t \) to time point \( t + 1 \) and \( \nu_1(t) \) is the process noise.

As the derivation of the Kalman filter continues it must be noted that the collected data is not continuous in time, as represented by the \( t \) variable in the above equations, but sampled. The fact the data is sampled is represented by using the variable \( n \) in place of \( t \). The process and measurement equations are now represented by:

\[
\begin{align*}
  h(n + 1) &= F(n + 1 | n)h(n) + \nu_1(n) & n = 1, 2, \ldots N \\
  y(n) &= X(n) \ast h(n) + \nu_2(n) & n = 1, 2, \ldots N
\end{align*}
\quad (4.3) \quad (4.4) \]

where the variables in bold represent matrices. The noise terms \( \nu_1 \) and \( \nu_2 \) are each modeled as zero-mean white noise processes with correlation matrices:

\[ E[\nu_i(n)\nu_i^T(k)] = \begin{cases} 
  Q_i(n), & n = k \\
  0, & n \neq k
\end{cases} \quad \text{for } i = 1 \text{ and } 2 \quad (4.5) \]

From the statement of the model, the noise terms have the properties of being uncorrelated with each other, the measured data and the underlying state of the system.

The start of Kalman Filter derivation begins with the prediction:

\[ \hat{y}(n | \mathcal{Y}_{n-1}). \quad (4.6) \]

This is the minimum mean-square estimate of the data at time point \( n \) given all data up to time point \( n - 1 \). Being an estimate there will be estimation error designated as the innovation process. This is:

\[ \alpha(n) = y(n) - \hat{y}(n | \mathcal{Y}_{n-1}) \quad (4.7) \]
The above states that the innovation $\alpha$ at point $n$ is equal to the data point $y$ at $n$ minus the prediction of $y$ at point $n$ based on all data up to point $n - 1$. The hat above $\hat{y}$, means that the value is a predication. This innovations process is also interpreted as the amount of new information that is contained in the newly acquired data point. The interpretation of new information is from the idea that there is a prediction of what $y$ at $n$ should be and any difference between the real $y$ and the prediction is new. The new information does not mean to imply that it is information to be confident in. It could be a measurement completely corrupted by noise.

The innovations process $\alpha$ has the following properties:

1. The innovations process is orthogonal to all past measurements.

$$E[\alpha(n)y^T(k)] = 0, \quad 1 \leq k \leq n - 1$$  \hspace{1cm} (4.8)

2. The innovations processes are orthogonal to each other.

$$E[\alpha(n)\alpha^T(k)] = 0, \quad 1 \leq k \leq n - 1$$  \hspace{1cm} (4.9)

3. There is a direct relationship between the measured data and the innovations.

The correlation matrix of the innovations is defined as:

$$R(n) = E[\alpha(n)\alpha^T(n)]$$  \hspace{1cm} (4.10)

and derived with the aid of another prediction variable, that of the state variable. The state variable has the prediction

$$\hat{h}(n|\gamma_{n-1})$$  \hspace{1cm} (4.11)

This, like the prediction of $y$, is the minimum mean-square estimate of the state at time $n$ based on all measurements up to time $n - 1$. Using the two prediction terms the
measurement Equation 4.4 can be rewritten as:

\[ \hat{y}(n|\mathcal{Y}_{n-1}) = X(n)\hat{h}(n|\mathcal{Y}_{n-1}) + \nu_2(n|\mathcal{Y}_{n-1}). \]  

(4.12)

Since the noise process is uncorrelated to the measurements its prediction is zero and drops out of the above equation, leaving:

\[ \hat{y}(n|\mathcal{Y}_{n-1}) = X(n)\hat{h}(n|\mathcal{Y}_{n-1}). \]  

(4.13)

Using the predicted measurement Equation 4.13, in the innovations Equation 4.7:

\[ \alpha(n) = y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1}) \]  

(4.14)

and then plugging in the measurement Equation, 4.4

\[ \alpha(n) = X(n)h(n) + \nu_2(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1}) \]  

(4.15)

factoring out \(X(n)\)

\[ \alpha(n) = X(n)[h(n) - \hat{h}(n|\mathcal{Y}_{n-1})] + \nu_2(n). \]  

(4.16)

Like the innovations being the error in the measurement variable prediction, there is error in the state variable prediction defined as:

\[ \varepsilon(n, n - 1) = h(n) - \hat{h}(n|\mathcal{Y}_{n-1}) \]  

(4.17)

This defines \(\varepsilon(n, n - 1)\) as the error in the state variable prediction at time \(n\) based on all data up to time \(n - 1\). Plugging the state error, Equation 4.17, into the innovations Equation 4.16, and this into the correlation matrix of the innovations, Equation 4.10, results in:

\[ R(n) = E[(X(n)\varepsilon(n, n - 1) + \nu_2(n))(X(n)\varepsilon(n, n - 1) + \nu_2(n))] \]  

(4.18)
Multiplying out all terms and distributing the expectation:

\[
R(n) = E[X(n)\epsilon(n, n-1)X^T(n)\epsilon^T(n, n-1)]
\]

\[+ E[\nu_2(n)X^T(n)\epsilon^T(n, n-1)] + E[X(n)\epsilon(n, n-1)\nu_2^T(n)] + E[\nu_2(n)\nu_2^T(n)] \quad (4.19)
\]

The second and third terms of Equation 4.19 are equal to zero because the measurement error, \(\nu_2\) is orthogonal to the predicted state-error. The fourth term is equal to the correlation matrix of the measurement noise, \(Q_2\). The resultant correlation matrix of the innovations process is therefore:

\[
R(n) = E[X(n)\epsilon(n, n-1)X^T(n)\epsilon^T(n, n-1)] + Q_2.
\quad (4.20)
\]

Rearranging terms yields:

\[
R(n) = X(n)E[\epsilon(n, n-1)\epsilon^T(n, n-1)]X^T(n) + Q_2.
\quad (4.21)
\]

thereby introducing the correlation matrix for the error in the state variable prediction:

\[
K(n, n-1) = E[\epsilon(n, n-1)\epsilon^T(n, n-1)].
\quad (4.22)
\]

The correlation matrix of the innovations is written as:

\[
R(n) = X(n)K(n, n-1)X^T(n) + Q_2
\quad (4.23)
\]

However this equation does hide an important feature which motivates the next step in the derivation. This is evident by rewriting \(R(n)\) out as:

\[
R(n) = X(n)[h(n) - \hat{h}(n|\gamma_{n-1})][h(n) - \hat{h}(n|\gamma_{n-1})]^TX^T(n) + Q_2
\quad (4.24)
\]

Upon writing the correlation matrix in this form two points are made. First, the prediction of the state variable is defined but its calculation is not made, and second, that the state variable \(h(n)\) is uncomputable.
Calculating the state variable prediction is addressed first. The state variable is predicted from the innovations process. This makes sense because the innovations process are directly related to the data, and the only known variables are the data, the design matrix and the transition matrix.

Consider the prediction of the state variable as a linear combination of past innovation values. The initial definition of the state variable in Equation 4.11 alludes to this. Recall that prediction at time $n$ is based on all past measurements up to time $n - 1$. Now this relationship on the past as a linear combination is defined

$$\hat{h}(n + 1|\mathcal{Y}_n) = G\alpha$$  \hspace{1cm} (4.25)$$

The linear combination matrix of past innovations, $\alpha$, is defined by $G$ in the above equation. Thinking of necessary matrix dimensions sheds some light on the relationships in the above equation. The state variable at the specific time point $n+1$ has dimensions of $(M \times 1)$. The predicted state variable is a function on the past innovations up to time $n$, the matrix size for $\alpha$ is $(n \times 1)$. Knowing this, the matrix $G$ must have dimensions $(M \times n)$. Note that the lower case value $n$ is used above. This indicates that not all of the data is acquired yet, and only acquired data is used. The innovations up to time $n$ are represented as $\alpha(1..n)$. This is not to be confused with $\alpha(n)$ which represents the innovation at time $n$.

The prediction of the state variable is the minimum mean-square error between it and the actual state variable, obtained by properly choosing $G$. Therefore if the problem is stated as:

$$h(n + 1) = G(1..n)\alpha(1..n)$$  \hspace{1cm} (4.26)$$

the optimum value of $G$ is then:

$$G(1..n) = E[h(n + 1)\alpha(1..n)]R^{-1}(1..n)$$  \hspace{1cm} (4.27)$$
Recall that Equation 4.25 is a linear combination, and is represented with summations

\[ \hat{h}(n + 1|\mathcal{Y}_n) = \sum_{k=1}^{n} G(1..k)\alpha(a..k) \]  

(4.28)

The summation can also be broken up as:

\[ \hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + \sum_{k=1}^{n-1} G(1..k)\alpha(1..k) \]  

(4.29)

This last step seems a bit of a stretch and is best explained with an example.

Given:

\[
\begin{bmatrix}
1 & 4 & 7 & 10 \\
2 & 5 & 8 & 11 \\
3 & 6 & 9 & 12 \\
\end{bmatrix}
\begin{bmatrix}
1 \\
2 \\
3 \\
4 \\
\end{bmatrix}
= 
\begin{bmatrix}
70 \\
80 \\
90 \\
\end{bmatrix}
\]  

(4.30)

Now applying the same technique as in Equation 4.29, the following should be correct:

\[
\begin{bmatrix}
1 & 4 & 7 \\
2 & 5 & 8 \\
3 & 6 & 9 \\
\end{bmatrix}
\begin{bmatrix}
1 \\
2 \\
3 \\
\end{bmatrix}
+ 
\begin{bmatrix}
10 \\
11 \\
12 \\
\end{bmatrix}
[4]
= 
\begin{bmatrix}
70 \\
80 \\
90 \\
\end{bmatrix}
\]  

(4.31)

and after multiplying out these matrices:

\[
\begin{bmatrix}
30 \\
36 \\
42 \\
\end{bmatrix}
+ 
\begin{bmatrix}
40 \\
44 \\
48 \\
\end{bmatrix}
= 
\begin{bmatrix}
70 \\
80 \\
90 \\
\end{bmatrix}
\]  

(4.32)

which is indeed correct. Now plugging Equation 4.27 into Equation 4.29 results in:

\[ \hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + \sum_{k=1}^{n-1} E[h(n + 1)\alpha(1..k)]R^{-1}(1..k)\alpha(1..k) \]  

(4.33)
and plugging in the process equation, Equation 4.3:

$$\hat{h}(n + 1|\mathcal{Y}_n) =$$

$$G(n)\alpha(n) + \sum_{k=1}^{n-1} E[[F(n + 1|n)h(n) + \nu_1(n)]\alpha(1..k)]R^{-1}(1..k)\alpha(1..k)$$

(4.34)

Recall that the process noise, $\nu_1(n)$ is orthogonal to the innovations, $\alpha(1..k)$. Taking this into account and rearranging terms:

$$\hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + F(n + 1|n) \sum_{k=1}^{n-1} E[h(n)\alpha(1..k)]R^{-1}(1..k)\alpha(1..k)$$

(4.35)

The definition of the gain, Equation 4.27, is evident in the above summation, resulting in:

$$\hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + F(n + 1|n) \sum_{k=1}^{n-1} G(1..k)\alpha(1..k)$$

(4.36)

where the summation term is the state variable prediction at time $n - 1$.

$$\hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + F(n + 1|n)\hat{h}(n|\mathcal{Y}_{n-1})$$

(4.37)

Being that the state variable prediction is the previous value plus a correction term the process is recursive. Taken in this form, the computer only has to store the previous single value of the state variable prediction and not all past values for time one to $n$. There is now an equation to calculate the prediction of the state variable. However, it still remains that the gain function, Equation 4.27, is dependent on the value of the real value of the state. This makes the gain function uncomputable. What follows will remedy this situation.

First, note the expectation $E[h(n + 1)\alpha(1..n)]$ remains uncomputable. Substituting the process Equation 4.3:

$$E[h(n + 1)\alpha(1..n)] = E[[F(n + 1|n)h(n) + \nu_1]\alpha(1..n)]$$

(4.38)

Distributing the above:

$$E[h(n + 1)\alpha(1..n)] = F(n + 1|n)E[h(n)\alpha(1..n) + \nu_1 \alpha(1..n)]$$

(4.39)
and recall that the innovations are orthogonal to the process equation.

\[
E[h(n+1)\alpha(1..n)] = F(n + 1|n)E[h(n)\alpha(1..n)]
\]  
(4.40)

Now substituting Equation 4.16 for the innovations and the state error, Equation 4.17, into the above:

\[
E[h(n+1)\alpha(1..n)] = F(n + 1|n)E[h(n)(X(n)\epsilon(n, n - 1) + \nu_2(n))]
\]  
(4.41)

First, recall that the process noise and the state variable are orthogonal. Then factor out the design matrix term, \(X(n)\) and substitute the state variable predication error written as:

\[
h(n) = \epsilon(n, n - 1) + \hat{h}(n|\gamma_{n-1})
\]  
(4.42)

into Equation 4.41

\[
E[h(n+1)\alpha(1..n)] = F(n + 1|n)E[\epsilon(n, n - 1)\epsilon(n, n - 1)^T + \hat{h}(n|\gamma_{n-1})(\epsilon(n, n - 1))X(n)]
\]  
(4.43)

The first term in the expectation is correlation matrix of the state variable prediction error and the second is zero. Using the above, the gain equation is rewritten as:

\[
G(n) = F(n + 1, n)K(n, n - 1)X^T(n)R^{-1}(n)
\]  
(4.44)

It seems that the gain equation is now no longer dependent of the process variable but is dependent on the transition matrix, design matrix and the correlation matrices of the innovations and the state variable prediction error. However, the correlation matrix of the state variable predication error is still dependent on the state variable.

The next step is to eliminate the state variable in the state variable prediction error term. Upon the completion of this step the Kalman filter derivation will be complete and computational.
Recall the equation for the state variable prediction error:

\[ \varepsilon(n, n-1) = h(n) - \hat{h}(n, \mathcal{Y}_{n-1}) \]  \hfill (4.45)

states that the error at time \( n \) is based on all past measurements up to time \( n - 1 \). Therefore the error in the state variable prediction at time \( n + 1 \) is:

\[ \varepsilon(n + 1, n) = h(n + 1) - \hat{h}(n + 1, \mathcal{Y}_n) \]  \hfill (4.46)

Substituting Equation 4.3 and Equation 4.37 into the above:

\[ \varepsilon(n + 1, n) = F(n + 1, n)h(n) + \nu_1 - (G(n)\alpha(n) + F(n + 1|n)\hat{h}(n|\mathcal{Y}_{n-1})) \]  \hfill (4.47)

Rearrange and substitute in the equation for the innovations, Equation 4.14

\[ \varepsilon(n + 1, n) = F(n + 1, n)(h(n) - \hat{h}(n|\mathcal{Y}_{n-1}) - G(n)[y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1})]) + \nu_1 \]  \hfill (4.48)

Substitute the measurement equation into the above

\[ \varepsilon(n + 1, n) = F(n + 1, n)(h(n) - \hat{h}(n|\mathcal{Y}_{n-1})) - G(n)(X(n)h(n) + \nu_2) \]

\[ -X(n)\hat{h}(n|\mathcal{Y}_{n-1})] + \nu_1 \]  \hfill (4.49)

Rearrange this to

\[ \varepsilon(n + 1, n) = F(n + 1, n)[h(n) - \hat{h}(n|\mathcal{Y}_{n-1})] - G(n)X(n)[h(n) - \hat{h}(n|\mathcal{Y}_{n-1})] \]

\[ -G(n)\nu_2(n) + \nu_1(n) \]  \hfill (4.50)

Upon rewriting a recursive nature is evident.

\[ \varepsilon(n + 1, n) = [F(n + 1, n) - G(n)X(n)]\varepsilon(n, n - 1) - G(n)\nu_2 + \nu_1 \]  \hfill (4.51)

This says the state prediction error at time \( n + 1 \) is a function of the state prediction error at time \( n \). The correlation of this is error term is now evaluated. Recall from Equation 4.22
that the correlation matrix of the error in the state variable prediction at time $n$ based on measurements up to time $n-1$ is:

$$K(n, n-1) = E[\epsilon(n, n-1)\epsilon^T(n, n-1)]$$ (4.52)

Therefore, the correlation matrix for the error in the process variable prediction is:

$$K(n+1, n) = E[\epsilon(n+1, n)\epsilon^T(n+1, n)]$$ (4.53)

Plugging Equation 4.51 into the above equation gives:

$$K(n+1, n) =$$

$$E[(F(n+1, n) - G(n)X(n))\epsilon(n, n-1) - G(n)\nu_2 + \nu_1)$$

$$(F(n+1, n) - G(n)X(n))\epsilon(n, n-1) - G(n)\nu_2 + \nu_1)]$$ (4.54)

Using property 7 from Appendix A, Equation 4.54 is rewritten as:

$$K(n+1, n) =$$

$$E[(F(n+1, n) - G(n)X(n))\epsilon(n, n-1) - G(n)\nu_2 + \nu_1)$$

$$(\nu_1)^T + \nu_2^T G^T(n) + \epsilon^T(n, n-1)[F(n+1, n) - G(n)X(n)]^T]$$ (4.55)
Multiply this out and distribute the expectation

\[ K(n+1, n) = \]

\[ E[(F(n+1, n) - G(n)X(n))\varepsilon(n, n-1)\varepsilon^T(n, n-1)(F(n+1, n) - G(n)X(n))^T] \]

\[ -E[G(n)v_2(n)\varepsilon^T(n)F(n+1, n) - G(n)X(n))^T] \]

\[ +E[v_1(n)\varepsilon^T(n, n-1)F(n+1, n) - G(n)X(n))^T] \]

\[ -E[(F(n+1, n) - G(n)X(n))\varepsilon(n, n-1)v_2^T(n)G^T(n)] \]

\[ +E[G(n)v_2(n)v_2^T(n)G(n)^T] \]

\[ -E[v_1(n)v_2^T(n)G(n)^T] \]

\[ E[(F(n+1, n) - G(n)X(n))\varepsilon(n, n-1)v_2^T(n)] \]

\[ -E[G(n)v_2(n)v_1^T(n)] \]

\[ +E[v_1(n)v_1^T(n)] \]  

(4.56)

Fortunately, the measurement, process and process prediction error are all orthogonal to each other. Taking this into account terms 2, 3, 4, 6, 7 and 8 are all equal to zero. Using the orthogonality and moving the expectations reduces the above to:

\[ K(n+1, n) = \]

\[ [F(n+1, n) - G(n)X(n)]E[\varepsilon(n, n-1)\varepsilon^T(n, n-1)]\varepsilon(n, n-1)]F(n+1, n) - G(n)X(n))^T \]

\[ +G(n)E[v_2(n)v_2^T(n)]G(n)^T \]

\[ +E[v_1(n)v_1^T(n)] \]  

(4.57)

Now recognize the above expectations as the correlation matrices of the error in the process prediction at time \( n \) based on data up to time \( n - 1 \), of the measurement noise and the
process noise, respectively. Again rewriting:

\[
K(n + 1, n) = \\
[F(n + 1, n) - G(n)X(n)]K(n, n - 1)[F(n + 1, n) - G(n)X(n)]^T + G(n)Q_2(n)G^T(n) + Q_1(n)
\] (4.58)

Use matrix properties 1, 2, 3, 7 and 9 from Appendix A to multiply out the first term in the above equation:

\[
K(n + 1, n) = \\
F(n + 1, n)K(n, n - 1)F^T(n + 1, n) - G(n)X(n)K(n, n - 1)F^T(n + 1, n) - F(n + 1, n)K(n, n - 1)X^T(n)G^T(n) + G(n)X(n)K(n, n - 1)X^T(n)G^T(n) + G(n)Q_2(n)G^T(n) + Q_1(n)
\] (4.59)

Now recall the equations for the gain as:

\[
G(n) = F(n + 1, n)K(n, n - 1)X^T(n)R^{-1}(n)
\]

whose transpose is:

\[
G^T(n) = R^{-1}(n)X(n)K^T(n, n - 1)F^T(n + 1, n)
\]

Which both are rewritten using matrix property 6 as:

\[
G(n)R(n) = F(n + 1, n)K(n, n - 1)X^T(n)
\] (4.60)

\[
R^T(n)G^T(n) = X(n)K^T(n, n - 1)F^T(n + 1, n)
\] (4.61)

Also recall the equation for the correlation matrix of the innovations:

\[
R(n) = X(n)K(n, n - 1)X^T(n) + Q_2(n)
\] (4.62)
which is rewritten as:

\[ R(n) - Q_2(n) = X(n)K(n, n - 1)X^T(n) \]  

(4.63)

and that correlation matrices are Hermitian, meaning they are equal to their transposes. This property is applied to the \( K(n, n - 1) \) matrix. Now Equation 4.61 is plugged into the second term of Equation 4.59, Equation 4.60 into the third term and Equation 4.63 into the fourth to get:

\[
K(n + 1, n) = 
F(n + 1, n)K(n, n - 1)F^T(n + 1, n) - G(n)R^T(n)G^T(n) \\
- G(n)R(n)G^T(n) + G(n)(R(n) - Q_2(n))G^T(n) \\
+ G(n)Q_2(n)G^T(n) + Q_1(n)
\]

(4.64)

In the above equation the fourth right hand term cancels out the third and fifth term leaving:

\[
K(n + 1, n) = 
F(n + 1, n)K(n, n - 1)F^T(n + 1, n) - G(n)R^T(n)G^T(n) + Q_1(n)
\]

(4.65)

This concludes the derivation of the Kalman filter.
4.1.1 Summary of Kalman Filter Derivation

This section summarizes the equations and variable introduced in Section 4.1. The measurements \( y(n) \) are the actual data and modeled with the measurement equation:

\[
y(n) = X(n)h(n) + \nu_2(n) \quad n = 1, 2, \ldots N
\]  

(4.66)

This states that \( N \) measurements are made, where \( X(n) \) is the known design matrix, which is analogous to the design matrix in linear regression. The variable \( h(n) \) is the state variable and modeled with the process equation:

\[
h(n + 1) = F(n + 1|n)h(n) + \nu_1(n) \quad n = 1, 2, \ldots N
\]  

(4.67)

This state variable changes from time points \( n \) to \( n + 1 \) via the known transition matrix \( F(n + n, n) \). This transition matrix allows for many types of behavior of the state variable, including but not limited to, random walk or autoregressive progression. The two equations also have respective noise terms, \( \nu_1(n) \) and \( \nu_2(n) \), modeled as zero-mean white noise processes. These two random variables are known \textit{a priori} and have their own respective correlation matrices, \( Q_2 \) and \( Q_2 \).

The prediction of the state variable starts from initial conditions for the state variable prediction \( \hat{h}(1|\mathcal{Y}_0) \) and the correlation matrix of the error in the state variable prediction, \( K(1, 0) \), then iterates on \( n \) up to \( N \) using:

\[
R(n) = X(n)K(n, n - 1)X^T(n) + Q_2(n)
\]

\[
G(n) = F(n + 1, n)K(n, n - 1)X^T(n)R^{-1}(n)
\]

\[
\alpha(n) = y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1})
\]

\[
\hat{h}(n + 1|\mathcal{Y}_n) = G(n)\alpha(n) + F(n + 1|n)\hat{h}(n|\mathcal{Y}_{n-1})
\]

\[
K(n + 1, n) = F(n + 1, n)K(n, n - 1)F^T(n + 1, n) - G(n)R^{-1}(n)G^T(n) + Q_1(n)
\]
One very interesting thing to point out is that the $R(n)$, $G(n)$ and $K(n + 1, n)$ matrices are all computable using only the known information. This means they are computable \textit{a priori} to the application of the filter. This observation has strong implications on the computational implementation and usage of this filter.

### 4.2 Implementation and Use of the Kalman Filter

After the derivation of the Kalman filter, the current discussion focuses on specifics to real world applications. The Kalman filter is a "general purpose" data analysis tool; for this reason it is worth describing it in terms of its intended application. Also required is a description of the methods used to estimate the variance terms, which were assumed known in the previous chapter. Finally, a method is needed to test whether the Kalman filter results make sense in light of the experimental task.

#### 4.2.1 Estimating the Variance Terms used in the Kalman Filter

Recall the equations that define the model:

\[
\begin{align*}
y(n) &= X(n)h(n) + \nu_2(n) & n = 1, 2, \ldots N \\
\nu_2(n) &\sim N(0, Q_2) \\
h(n + 1) &= F(n + 1|n)h(n) + \nu_1(n) & n = 1, 2, \ldots N \\
\nu_1(n) &\sim N(0, Q_1)
\end{align*}
\]

The first simplification is to model the progression of the state variable as a random walk. This is the simplest choice of models and is chosen for parsimony and its precedence in the fMRI literature [11]. This is implemented by setting the transition matrix $F(n + 1|n)$, to be the identity matrix [43]. The second, is to rewrite the variance of the state noise term, $\nu_1(n)$, as a fraction of the measurement noise [43]. Therefore, Equations 4.68 and 4.69 are
rewritten as:

\[ y(n) = X(n)h(n) + \nu_2(n) \quad n = 1, 2, \ldots N \]  
(4.70)

\[ \nu_2(n) \sim N(0, \sigma^2) \]

\[ h(n + 1) = h(n) + \nu_1(n) \quad n = 1, 2, \ldots N \]  
(4.71)

\[ \nu_1(n) \sim N(0, \sigma^2 P) \]

With the variance term, \( \sigma^2 \), explicitly written, the Kalman filter equations are [43]:

\[ \sigma^2 R(n) = X(n)\sigma^2 K(n, n - 1)X^T(n) + \sigma^2 \]

\[ \sigma^2 G(n) = \sigma^2 K(n, n - 1)X^T(n)\sigma^2 R^{-1}(n) \]

\[ \alpha(n) = y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1}) \]

\[ \hat{h}(n + 1|\mathcal{Y}_n) = \sigma^2 G(n)\alpha(n) + \hat{h}(n|\mathcal{Y}_{n-1}) \]

\[ \sigma^2 K(n + 1, n) = \sigma^2 K(n, n - 1) - \sigma^2 G(n)\sigma^2 R^{-1}(n)\sigma^2 G^T(n) + \sigma^2 P \]

Explicit writing of the variance term allows its easy removal, producing further simplifications. The Kalman filter equations excluding the variance term are rewritten as:

\[ R(n) = X(n)K(n, n - 1)X^T(n) + 1 \]  
(4.72)

\[ G(n) = K(n, n - 1)X^T(n)R^{-1}(n) \]  
(4.73)

\[ K(n + 1, n) = K(n, n - 1) - G(n)R^{-1}(n)G^T(n) + P \]  
(4.74)

These iterative updates are independent of data and now only have one unknown parameter, \( P \).

Recall again, the innovations sequence and the significance of these values:

\[ \alpha(n) = y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1}) \]  
(4.75)
The innovations are the error between the data, $y(n)$ and the estimate of the state, $\hat{h}(n|\mathcal{Y}_{n-1})$, convolved with the model, $X(n)$. This process is also thought of as the amount of new information contained in each data point [9]. Therefore, to minimize this error, the parameters, $\sigma^2$ and $P$ must be chosen properly. By recognizing that the innovations are a Gaussian random variable this is done via a maximum likelihood approach of the innovations [43, 44, 11]. The innovations have a mean of zero and a covariance defined above as $\sigma^2 R(n)$. Therefore the likelihood, or probability, of obtaining the value $\alpha$ at time $n$ given $\sigma^2$, $P$ and $\hat{h}$ is:

$$pr(\alpha; \sigma^2, P, \hat{h}(n|n-1)) = \frac{1}{\sqrt{2\pi \sigma^2 R(n)}} \exp\left(\frac{-\alpha^2(n)}{2\sigma^2 R(n)}\right) \tag{4.76}$$

where $P$ and $\hat{h}(n|n-1)$ are intrinsic functions of $\alpha$ and $R$. The likelihood, or probability of obtaining $\alpha$ after collecting $N$ data points is the product of the probabilities at each individual point. As shown:

$$L(\alpha(n); \sigma^2, P, \hat{h}(n|n-1)) = \prod_{n=1}^{N} \left(\frac{1}{\sqrt{2\pi \sigma^2}} \exp\left(\frac{-\alpha^2(n)}{2\sigma^2 R(n)}\right)\right) \tag{4.77}$$

The aim is to maximize the log-likelihood of Equation 4.77 thereby finding the value of $P$ that minimizes the value of $\alpha$.

The natural logarithm of Equation 4.77 is taken to produce:

$$\ln L \left(\alpha(n); \sigma^2, P, \hat{h}(n|n-1)\right) = -\sum_{n=1}^{N} \frac{1}{2} \ln(2\pi \sigma^2 R(n)) + \sum_{n=1}^{N} \frac{-1}{2} \frac{\alpha^2(n)}{R(n)\sigma^2} \tag{4.78}$$

and simplified as:

$$\ln L \left(\alpha(n); \sigma^2, P, \hat{h}(n|n-1)\right) = \tag{4.79}$$

$$-\frac{1}{2} \sum_{n=1}^{N} \ln(2\pi) - \frac{1}{2} \sum_{n=1}^{N} \ln(\sigma^2) - \frac{1}{2} \sum_{n=1}^{N} \ln(R(n)) - \frac{1}{2} \sum_{n=1}^{N} \frac{\alpha^2(n)}{R(n)\sigma^2}$$
\[
\ln L ( \alpha(n); \sigma^2, P, \hat{h}(n|n - 1) ) = \frac{-N}{2} \ln(2\pi) - \frac{N}{2} \ln(\sigma^2) - \frac{1}{2} \sum_{n=1}^{N} \ln R(n) - \frac{1}{2} \sum_{n=1}^{N} \frac{\alpha^2(n)}{R(n)\sigma^2}
\]

Equation 4.81 is the log-likelihood of \( \alpha \) given \( \sigma^2, P \) and \( \hat{h}(n|n - 1) \) which now needs maximization of the parameters \( \sigma^2 \) and \( \hat{h}(n|n - 1) \). Maximization involves taking the partial derivative of the log-likelihood Equation 4.81 with respect to the two parameters of interest and setting the result equal to zero. Solutions with regard to the parameter of interest are substituted back into the log-likelihood Equation 4.81 resulting in a concentration with respect to the parameters of interest.

\[
\frac{\partial \ln L}{\partial \hat{h}(n|n - 1)} = 0 = -\sum_{n=1}^{N} \frac{2\alpha(n)}{\sigma^2 R(n)} \frac{\partial \alpha(n)}{\partial \hat{h}(n|n - 1)}
\]

Recall again the innovation sequence:

\[
\alpha(n) = y(n) - X(n)\hat{h}(n|\mathcal{Y}_{n-1})
\]

whose partial derivative is:

\[
\frac{\partial \alpha(n)}{\partial \hat{h}(n|n - 1)} = -X(n)
\]

Therefore plugging Equations 4.83 and 4.84 into Equation 4.82 results in:

\[
\frac{\partial \ln L}{\partial \hat{h}(n|n - 1)} = 0 = -\sum_{n=1}^{N} \left( y(n) - X(n)\hat{h}(n|n - 1) \right) \frac{(-X(n))}{\sigma^2 R(n)}
\]

Using relationship 9 and distributing, the summation results in:

\[
\frac{\partial \ln L}{\partial \hat{h}(n|n - 1)} = 0 = \sum_{n=1}^{N} \left( \frac{X^T(n)y(n)}{\sigma^2 R(n)} \right) - \sum_{n=1}^{N} \left( \frac{X^T(n)X(n)\hat{h}(n|n - 1)}{\sigma^2 R(n)} \right)
\]

The summations are removable by rewriting in terms of matrices and bringing the \( R \) term from the denominator to the numerator as:

\[
\frac{X^T R^{-1} y}{\sigma^2} = \frac{X^T R^{-1} X \hat{h}}{\sigma^2}
\]
The $\sigma^2$ terms in the denominators cancel out resulting in:

$$X^T R^{-1} y = X^T R^{-1} X \hat{h}$$ \hspace{1cm} (4.88)

To solve for $\hat{h}$ each side of Equation 4.88 is left hand multiplied by $(X^T R^{-1} X)^{-1}$, to result in:

$$\hat{h} = (X^T R^{-1} X)^{-1} X^T R^{-1} y$$ \hspace{1cm} (4.89)

This solution agrees with the solution obtained in Cooley and Prescott 1976 [44] in their Equation 2.19 and with the linear regression solution once all data is collected as shown in [47].

The next step is to find an estimate of $\sigma^2$ by following a similar procedure; therefore the partial derivative of the log-likelihood Equation 4.81 is taken with respect to $\sigma^2$:

$$\frac{\partial \ln L}{\partial \sigma^2} = 0 = -\frac{N}{2} \frac{1}{\sigma^2} + \frac{1}{2} \sum_{n=1}^{N} \frac{\alpha^2(n)}{R(n) \sigma^2}$$ \hspace{1cm} (4.90)

Using the equation for the innovations 4.83, rewriting in terms of matrices and rearranging:

$$\frac{N}{2} \frac{1}{\sigma^2} = \frac{1}{2} \frac{(y - X \hat{h})^T R^{-1} (y - X \hat{h})}{(\sigma^2)^2}$$ \hspace{1cm} (4.91)

Solving for $\sigma^2$:

$$\sigma^2 = \frac{1}{N} (y - X \hat{h})^T R^{-1} (y - X \hat{h})$$ \hspace{1cm} (4.92)

This solution agrees with the solution obtained in Cooley and Prescott 1976 [44] in their Equation 2.20. To concentrate the log-likelihood equation the estimates of $\hat{h}$ (Equation 4.88) and $\sigma^2$ (Equation 4.92) are plugged into Equation 4.81.

$$\ln L^*(\alpha; P) = -\frac{N}{2} \ln 2\pi - \frac{N}{2} \ln \sigma^2 - \frac{1}{2} \sum_{n=1}^{N} \ln R(n) - \frac{1}{2} \frac{\alpha^T R^{-1} \alpha}{\hat{h}^T (y - X \hat{h})^T R^{-1} (y - X \hat{h})}$$ \hspace{1cm} (4.93)

Substituting in Equation 4.83 for $\alpha$ results in obvious simplifications:

$$\ln L^*(\alpha; P) = -\frac{N}{2} \ln 2\pi - \frac{N}{2} \ln \sigma^2 - \frac{1}{2} \sum_{n=1}^{N} \ln R(n) - \frac{N}{2} \frac{(y - X \hat{h})^T R^{-1} (y - X \hat{h})}{(y - X \hat{h})^T R^{-1} (y - X \hat{h})}$$ \hspace{1cm} (4.94)
Therefore the concentrated log-likelihood function is written as:

\[
\ln L^*(\alpha; P) = -\frac{N}{2} \ln 2\pi - \frac{N}{2} \ln \hat{\sigma}^2 - \frac{1}{2} \sum_{n=1}^{N} \ln R(n) - \frac{N}{2}
\]

\[
= -\frac{N}{2} (\ln 2\pi + 1) - \frac{N}{2} \ln \hat{\sigma}^2 - \frac{1}{2} \sum_{n=1}^{N} \ln R(n)
\]  \hspace{1cm} (4.95)

which agrees with the solution obtained in Cooley and Prescott 1976 [44] and Garbade 1977 [43], to within a constant. Maximization of the log-likelihood Equation 4.95 with respect to \( P \) will result in the value of \( P \) that minimizes the error between the data, \( y \) and the estimate \( \hat{X} \). This maximization is complicated by \( \hat{\sigma} \) (Equation 4.92) being a function of \( P \), and \( R \) (Equation 4.72) being a function of \( P \) via \( K \) (Equation 4.74). Therefore, numerical methods were employed for the maximization, namely the MatLab function \texttt{fminbnd}. This function finds the value of \( P \) that maximizes Equation 4.95 within specified bounds. Once an optimum estimate of \( P \) is found it is plugged into Equation 4.92 to find an estimate of the total variance \( \hat{\sigma}^2 \).

4.2.2 Modifications for the Use with FMRI Data

As discussed in the previous section, the maximum likelihood (ML) method is employed to estimate the values of the variances of the measurement noise and the state variable noise terms. The use of this method in combination with Kalman filtering was developed by Cooley and Prescott 1976 [44], used by Garbade 1977 [43] and used with fMRI by Buchel and Friston 1998 [11]. The method employed in the three works deal with variable parameter regression.

Variable parameter regression (VPR) uses a first order Kalman filter model to perform regression, where the regression coefficient varies in time. A first order Kalman filter uses the following model:

\[
y(n) = (X(n) * h)\beta(n) + \nu_2(n)
\]  \hspace{1cm} (4.96)
where $y$ is the data, $(X(n) * h)$ is the design vector $X$ convolved with a model of the hemodynamic response function $h$ times a regression coefficient $b$ plus measurement noise. The only difference between this model and that used in “standard” statistical parametric mapping [14] is the dependance of the regression coefficient as a function of time. This regression coefficient is the state variable and is modeled as a random walk:

$$h(n + 1) = h(n) + \nu_1(n)$$  \hspace{1cm} (4.97)

This is the exact implementation as done before in the literature [11]. It is assumed that the only variance between the design model and the data is either measurement noise or process variance. Therefore, the design model must be accurate. The design model in this case is a convolution between the experimental design, the on/off paradigm, and a model of the hemodynamic response function. As with linear regression if there is error in either of these models it is propagated to the regression coefficients.

The technique of VPR, or first order Kalman filtering, makes the same assumptions often made in standard general linear modeling of fMRI data. These are the assumptions that the model of the underlying hemodynamic response function is stationary and accurate. That is, it does not change in shape over the course of the experiment. Accuracy relates to the actual shape of the response and the width. Since the system is modeled as a convolution of a response function and an input signal, one needs to assume that the neuronal response to a stimulus closely follows the stimulus. In summary, by using the input stimulus as a model of neuronal activity and a standard model of the hemodynamic response to that activity, the following assumptions are made: the neuronal response occurs for the same amount of time as the stimulus, the hemodynamic response in the experiment of interest is the same shape as a standard model and that the hemodynamic response does not vary in shape or amplitude over the experiment.

To overcome these assumptions a fourteenth order Kalman filter is used. The choice of this order length is based on the hypothetical timing parameters of the hemodynamic
Figure 4.1 Hypothetical response to a twelve second stimulus used to determine filter order. Circles represent when a scan is acquired.

response function in response to a twelve second stimulus. The results is that the response takes thirty-nine seconds to return to baseline levels. This is shown in Figure 4.1. Recall that the repetition time, or time it takes to acquire a single image of the brain, is three seconds. Therefore, it will take fourteen images of the brain to acquire the entire temporal progression of the response to a twelve second stimulus.

The state space vector, $h$ in Equation 4.97, having 14 time points has a temporal length of 42 seconds. This allows sufficient time for the response to a 12 second stimulus to pass through all of its dynamics. The model used in this case only encodes the start times of presented stimuli, $X$ in Equation 4.96. Therefore, no assumptions are made with regards to the length of the neuronal response. Since the filter estimates the state vector at every time point the result of this analysis is an estimate of the hemodynamic response as it progresses throughout the experiment.
The method described above of determining estimates of the underlying variances, $\sigma^2$ and $P$ was developed to determine if regression coefficients were stable or not [43, 44]. In adapting this technique to functional brain imaging data some considerations need to be met. The method is an iterative search method; therefore, each iteration processes the entire time series through the Kalman filter. Implementing this on long time series on a voxel by voxel basis is computationally impractical.

To avoid this computing impracticality, a training set of data is used to train the filter before test data is analyzed. The training data may be the beginning of a run of data, or a separate session of data. From this training set, values of $\sigma^2$ and $P$ are determined on a voxel-wise basis and used to analyze the test data.
CHAPTER 5
SPECIFIC AIMS

The overall goal of this dissertation is to extract time varying behavior from fMRI data using the Kalman filter. The filter has proven quite useful for use in other fields, such as RADAR tracking, financial tracking and as the foundation for neural networks. Such diverse applications exemplify the utility of the method and this dissertation is a validation of this method’s applicability to analysis of fMRI data.

5.1 Statement of Aims

The goal of this work was addressed with six specific aims, these are as follows.

1. Specific Aim 1: To show that without prior information of the temporal profile of a signal, the proposed method distinguished sustained stimuli, transient stimuli and noise from a voxel showing no task related signal change. This aim was implemented with the analysis of data from subjects performing flashing checkerboard experiments for either sustained (12 seconds) or transient (2 seconds) periods of time.

   - Hypothesis 1 Without prior knowledge of the expected temporal response profile, the proposed method extracts differential responses that agree with the two different stimulus presentations.
   
   - Secondary Hypothesis The extracted response from voxels showing no task related signal change will have temporal characteristics unlike those expected from a sustained or transient response.

2. Specific Aim 2: To distinguish between primary and secondary olfactory cortices which are known to evoke differential temporal profiles to odorant stimuli. This goal will be implemented with the analysis of data from subjects performing a odorant stimulation experiment.
• **Hypothesis 2** Without prior knowledge of the expected temporal response profile, the proposed method will extract differential responses to olfactory stimuli in the primary and secondary olfactory cortices.

3. **Specific Aim 3:** To show that using a priori information about the underlying response in a brain region will improve statistical maps as compared to other statistical models.

• **Hypothesis 3** The incorporation about the underlying response in a brain region as determined using the Kalman filter will improve statistical maps as compared to models incorporating no a priori information.

4. **Specific Aim 4:** To show that using the Kalman filter time dependent changes can be extracted.

• **Hypothesis 4** There are time dependent changes over the experiment which the adaptive approach employed in this work does detect, that standard linear regression models do not.

Secondary Aims

1. **Specific Aim 5:** To show that the Kalman filter is dependent on the data it is trained on.

• **Hypothesis 5** When the Kalman filter is trained on data from a different experimental source it will not perform as well as being trained on data from a similar source.

2. **Specific Aim 6:** To show that as the Kalman filter is trained on more data the prediction error decreases.

• **Hypothesis 6** As the amount of data increases the Kalman filter's estimate will gain confidence.
5.2 Methods to Address Aims

The specific aims of this work were addressed with data collected from ten subjects whose demographics are discussed later in the methods chapter. These ten subjects were all scanned at the Hatch Center for MR Research in the Neurological Institute at Columbia University on a Philips Medical Systems Intera 1.5 Tesla Research machine. All subjects were scanned four times during the odorant stimuli, nine of these subjects were scanned once during transient visual stimulus, seven were scanned twice during the sustained visual stimulus. The specific aims were addressed within twenty regions of interest (ROI).

The ROIs used in these analyses were taken from the literature as those previously involved in olfactory or visual experiments [4][48][34][49]. See the work by Poellinger et al 2001 for an excellent description of the regions of interest for an fMRI olfactory experiment. The ROIs are shown in Appendix C.

5.2.1 Specific Aim 1

This aim focuses on the application of the Kalman filter to data from visual stimuli experiments. The aim is to show that with very robust experimental stimuli the proposed method extracts the expected responses from expected locations. This lays the ground work for the second specific aim when the Kalman filter is applied to less robust stimuli, namely odorants.

The visual experiment consists of two stimuli, a two second flashing checkerboard (the transient stimulus) and a twelve second flashing checkerboard (the sustained stimulus). The basis for these choices is derived from the olfactory literature, where the response to odorants has shown differential temporal responses [3][4] across brain regions. These responses are a rapidly habituating one occurring at the beginning of the odorant presentation and a sustained response in time [2]. Since these differential responses are expected in the olfactory data, the Kalman filter method is first tested to ensure its ability to extract these differential responses. This is done with data from the visual experiment.
The first step in addressing this aim is to test whether the experimental stimulus elicited task related signal change. This is done using a standard general linear model (GLM) analysis to produce statistical parametric maps [14]. The model used for the GLM analysis of the sustained visual data is a stimulus design with a 12 second “on” period and a 30 second “off” period convolved with the difference of two gamma functions model of the HRF. The transient visual stimulus data is analyzed using a model with a 2 second “on” period and a 40 second “off” period convolved with the difference of two gamma functions model of the HRF. The results from this analysis are shown later in Section 7.2.1.

The data from each ROI (twenty in all), in both hemispheres, in every subject are averaged for each experimental run. The result is forty time series per run, per subject. Data from all averaged time series are processed with the fourteenth order Kalman filter. The filter uses the time series data and a model of the stimulus. This stimulus model only incorporates the start of a visual presentation. Therefore, for each run of visual stimuli, this vector contains all zeros except at the start of each visual stimulus block where it has a value of one.

The output of this filter is a vector of length fourteen, which corresponds to 39 seconds, for every experimental time point. Therefore, for one run of data containing eighty time points, this output matrix contains eighty vectors, each of length thirty nine seconds, or 14 points, long. The last vector in the experimental run is used as the estimate of the underlying task related response. This is chosen because at this time point all data has been included in generating its estimate.

From each ROI in every subject the width of the response is measured at half its maximal value, (the FWHM). The width is hypothesized to differ between the data from the transient stimulus and the sustained stimulus. The extracted widths are compared within ROI, and hemisphere, and across experimental stimuli. Successful distinction between the visual stimuli will show that the Kalman filtering method is appropriate for appli-
cation to the odorant stimuli data. The results from this specific aim are in shown later in Section 7.2.3.

5.2.2 Specific Aim 2

This aim focused on the application of the Kalman filter to data from olfaction experiment. The timing parameters for the odorant stimuli are the same as for the sustained visual stimulus, 12 seconds “on” and 30 seconds “off.” The Kalman filter analysis was exactly the same as in the visual experiment; however the hypothesis was different. Instead of the extracted response differing between stimuli, it was expected to differ between brain regions.

The first step in addressing this aim was to test whether the experimental stimulus elicited task related signal change. This was done using a standard general linear model (GLM) analysis to produce statistical parametric maps [14]. The model used for this analysis was that described in Section 3.1. This is the incorporation of an exponential decay and the three basis functions.

The analyses were done in the same ROIs as the visual experiment and the widths of the responses were compared in the same manner. The results from this specific aim are shown later in Section 7.3.2.

5.2.3 Specific Aim 3

Training on Data from Session One to test Session Two This aim was used for testing the Kalman filter’s estimate of the underlying response at improving statistical analysis of fMRI data as compared to other models. These comparisons were tested on data from the second session of data once the models were trained, where appropriate, on data from session one. There were seven models included in this analysis, the experimental stimulus timing (12 seconds on, 30 seconds off), a six second delayed version of the experimental stimulus, the experimental timing convolved with a single gamma function, the experimental timing convolved with the double gamma model, a model with a shortened on time
convolved with the double gamma model (6 seconds on and 36 seconds off), the fit from the previous sessions' data to a model with a rapidly decaying exponential function convolved with three optimal basis functions, and a model created from the estimate of the underlying signal as derived from the previous run of data using the Kalman filter. Examples of these seven models are shown in Figure 7.11.

Figure 5.1 The seven designs compared for variance accountability. The design shown for Kalman filter analysis is only an example.

The single regressor models of the above set, the first five, were tested on the second session of data. This is because the dependent variable used for model comparison, the percent variance accounted for, is not dependent on the scaling of the model. The three regressor basis set was fit to the first session of data. This best estimate of the data was used as a model for the second session of data. The Kalman filter derived model is based on the training of the filter on session one's data and tested on session two. The model comparisons are therefore all based on the percentage of variance accounted for in the second session of data using models trained on the first session.

The models were compared across twenty regions of interest (ROI). The data from each run was averaged on a voxel wise basis across the ROI. The ROIs used along with
their abbreviations, as used in the figures, are Brodmann Area 17 (BA17), Brodmann Area 18 (BA18), amygdala (amyg), anterior cingulate (AC), calcarine sulcus (calc), entorhinal (entorhinal), inferior frontal orbital (f int orb), middle frontal orbital (f mid orb), superior frontal orbital (f sup orb), fusiform (fus), hippocampus (hip), insula (ins), middle cingulate (mid cing)m olfactory cortex (olf), the combination of the frontal orbit and Brodmann area 47 (f orb/BA47), parahippocampus (parahipp), posterior cingulate (post cing), temporal pole (temp pole) and the thalamus (thal). These ROI overlaid on an anatomical high resolution image are shown in Appendix C along with a description of the method of their creation. The third factor in the ANOVA is HEMISPHERE. Each ROI was either in the left or the right hemisphere.

The ANOVA therefore had four factors: SUBJECT, METHOD, ROI, and HEMISPHERE. SUBJECT was a random factor, for each subject was randomly drawn from the population of healthy young adults. The demographics are presented later in Section 6.1. The other three factors were all fixed. The numbers of levels for each factor were: 7 for METHOD, 20 for ROI and 2 for HEMISPHERE. The dependent variable was the percent of variance accounted for by a model. This was calculated via linear regression as follows.

$$y = X\beta + \nu$$  \hspace{1cm} (5.1)

where $y$ is the data vector, $X$ is the design matrix to test, $\beta$ are the beta weights and $\nu$ is measurement noise. Estimates of the beta weights are found as follows:

$$\hat{\beta} = (X^TX)^{-1}X^Ty.$$  \hspace{1cm} (5.2)

The variance not accounted for by the model is found from the variance of the residual after estimating the data, where the residuals are

$$residuals = y - \hat{y} = y - X\hat{\beta}.$$  \hspace{1cm} (5.3)
The percentage of variance accounted for by the model is therefore found as

\[
\text{Percentage variance accounted for} = \left(1 - \frac{\text{var(residuals)}}{\text{var(data)}}\right) \times 100 \quad (5.4)
\]

Main effects were tested to determine if METHOD, ROI or HEMISPHERE accounted for a significant amount of variance between observations. First level interactions were tested to determine if there were significant relationships between two factors. Post-hoc tests were done to determine how significant differences between levels were.

The post-hoc testing was done using the Scheffé procedure. This tests all linear combinations of pairs between the factor levels and determines their confidence intervals for a critical value of 0.05. Those comparisons whose confidence intervals do not contain the value zero are deemed significantly different from zero with a one in twenty chance of being incorrect.

Once pairs of levels were deemed significantly different from each other, a two sample t-test was done between them to determine an actual probability of the means being equal. The Scheffé test only determines which means are different at a critical value of 0.05. The t-test gives the actual probability.

The post-hoc Scheffé tests were done for all significant effects or interactions; however, the post-hoc t-tests were not done for the ROI differences. This is because the multitude of ROIs can lead to a level being significantly different from up to nineteen other levels. Therefore, these results are described in terms of the top three most significant ROIs and what other ROIs they differ from. Since only the post-hoc Scheffé tests were done with the ROI factor, there is at least 95% confidence in their difference. The results from this specific aim are shown later in Section 7.4.

Specific Aim 3.1 The third aim will again be addressed; however, across hemispheres. As the overall aim of this work is to extract time varying behavior, testing across sessions of data may be confounded by the main effect of interest, the time variance. To circumvent
this, the seven models described in Specific Aim 3, will be trained on one hemisphere and tested on the opposite hemisphere. This analysis will be performed within session. The result is that time varying effects will not confound the analyses, assuming the temporal effects affect both hemispheres similarly. These analyses used models and tests identical to those previously described, and were performed on all sessions of data. The results are shown in Section 7.4 and Appendix B.

5.2.4 Specific Aim 4

This aim is to extract effects of time. Up to this point the Kalman filter has only been used to extract a single model of the underlying response to a stimulus. This does not take advantage of the filter’s main ability, to track a signal over time. Instead of making predictions about the underlying response to improve statistical models, the Kalman filter is applied to track the signal. The application is identical to that used in the previous sections however the results are used differently. The response at every time point are used to investigate time dependent changes.

Many models can be used here to detect time dependent changes, and the one chosen for this olfactory experiment is a single exponential. This is a parsimonious model allowing for easy interpretation and has precedence in the literature. Sobel et al. [3] predicted an exponential decay in their data and created a regressor to model it. This is a different exponential decay that that used to create the exponentially decaying statistical model. This decay is an across experiment decay.

To determine if there is such decay in the data used here, the peak response across experimental time is extracted from the Kalman filters’ estimated responses. From this peak response data, the following model is applied:

\[
data = a \cdot exp(b \cdot t)\]

where the decay parameter, \(b\), is of interest. The value of \(b\) is estimated using a data transformation and linear regression. The natural logarithm is taken of both sides of Equation 5.5
resulting in:

\[ \ln(data) = a + b \cdot t. \] (5.6)

This transformation converts the non-linear regression model of Equation 5.5 into a linear one, where estimation of \( b \) is straightforward.

For each ROI and HEMISPHERE in each subject these values of \( b \) were determined. These results were entered in an ANOVA to determine if any ROI or HEMISPHERE showed significantly greater rates of decay than the other ROIs or HEMISPHERE. The results from this specific aim are shown later in Section 7.5.

**Specific Aim 4.1** Once the exponential model was fit to the data, the model comparison analyses of Specific Aim 3.1 were redone to include this information. This time the decaying information was included to create an eighth model. This model was the Kalman filter estimate model multiplied by the exponential fit. These analyses were performed across hemispheres, within session for the olfactory data. The results from these two additional analyses are combined and shown in Section 7.5.1.

**5.2.5 Specific Aim 5**

This aim was to show that the Kalman filter was dependent on its training data. This step was required to validate that the results of the Kalman filter were dependent on the data being tested and not the result of a bias intrinsic to the method. This analysis only varied the stimulus and tested within subjects and within ROI. The within subject and within ROI restrictions ensured that the noise structures were the same across comparisons.

Two ROI were chosen, Brodmann Area 17, a typical visual stimulus ROI and the piriform cortex, a typical olfaction ROI. Working on each ROI separately, the Kalman filter was trained on either visual stimulus data or olfactory data. The extracted response from the training data was used to create a test design for the test data. A second run of data, with the same stimulus, was then tested within the ROI using the training information. The
percentage of variance explained by this model was then used an independent variable in an analysis of variance. The expected results from this analysis were that when the filter was trained on the visual data, in the visual ROI, it will make the best prediction of the response in the test visual data. This was also true for the olfactory data and olfactory ROI.

Testing these hypotheses was done with two separate ANOVA models, one for the olfactory ROI (the piriform) and one for the visual ROI (BA 17). There were three factors in this analysis each having two levels. The factors were hemisphere, with left and right levels, training data, with visual and olfactory as levels, and test data, with visual and olfactory data as levels. The results from this specific aim are shown later in Section 7.6.

5.2.6 Specific Aim 6

The design of the Kalman filter was to minimize the error in its estimates as data becomes available. Therefore, Kalman filter estimates of the response have decreasing error as experimental time elapses. This was shown by example, with estimated responses and the error of the estimate as intrinsically determined by the Kalman filter using data from the group mean. The results from this specific aim are shown later in Section 7.7.
CHAPTER 6

METHODS

Following the previous discussion of the aims of this experiment, the subjects and general methods of the overall experiment are discussed. This includes discussion of the programs used for stimuli presentation, the hardware to present the odorant stimuli, the functional scanning setup and the imaging data analysis.

6.1 Subjects

Ten subjects were scanned in this experiment, six male, one left handed. Their ages ranged from 18 to 52 years old with a mean and standard error of 26.6 (1.04). All subjects were scanned four times during the odorant stimuli, nine subjects were scanned once during transient visual stimulus, and seven subjects were scanned twice during the sustained visual stimulus. All scanning occurred at the Hatch Center for MR Research in the Neurological Institute at Columbia University on a Philips Medical Systems Intera 1.5 Tesla Research machine. The study was approved by the New York State Psychiatric Institute IRB and the Columbia Presbyterian Medical Center IRB.

6.2 Experimental Setup

The experimental setup that follows is the sequence of events that take place the day the research subject is scanned. This was the setup for the behavioral testing and functional MRI imaging, one of the key features is the of paced breathing.

Paced breathing is used to ensure adequate sampling of the presented odors. Odors are presented for twelve seconds at at time making it imperative for paced breathing. At a rate of ten breaths per minute, one breath takes six seconds, as shown in Figure 6.1. At this rate, the subject can inhale the odor at most twice. If the subject is breathing at a rate of twelve breaths per minute, one breath takes five seconds. Therefore, two or three
inhalations may be taken during the odor presentation, as shown in Figure 6.2. A greater breathing rate than 12 would provide more odor inhalations per odor presentation; however, it becomes impractical for subjects in a supine position in the MRI. The rate of ten breaths per minute is also set as a lower limit to ensure a minimum of two odor inhalations per minute.

6.3 Paced Breathing Practice

Approximately one hour before the scan, the subject is trained with paced breathing to chose a comfortable rate, either 10, 11 or 12 breaths per minute. To practice, the subject interacts with the LabView program Assess_Practice_Paced_Breathing, found in Appendix D.8. The program is set up to display on two monitors allowing a subject viewing monitor and an experimenter monitor. With this, the subject has a simple screen to focus on, while the experimenter views the programmatic controls and the subject’s
breathing trace. The subject views a "breathing pacer," which is a tank that fills and empties with sinusoidal movements at the rate set by the experimenter.

During this test, the subject is fitted with dual cannula. The dual cannula is able to present odors to the subjects' nostrils and assess breathing. One cannula is connected to the olfactometer and the other to the breathing transducer. The olfactometer is discussed later in Section 6.6. The transducer is sampled at a rate of 10 samples per second via the Mini-Lab from Measurement Computing Corporation, (16 Commerce Boulevard, Middleboro, MA 02346). This is a digital to analog converter that works via the computer's USB port.

The experimenter sets the breathing rate to eleven breaths per minute and a run time for two minutes. After the two minutes has elapsed, the program calculates the breathing rate. To do this the Fourier Transform is taken of the breathing data. The real part of this result is tested for the location of the largest peak. The hypothesis is that the breathing rate is the dominant frequency in the frequency domain. The peak detection is done with
LabView's built-in Peak Detector.vi program to detect peaks with a width of at least 3 points. The width parameter is used to prevent anomalous spikes from being confused with the dominant frequency. In addition to the frequency domain peak detection, the user can also count breaths per minute from the time course display.

After breathing at eleven breaths per minute, the subject is asked whether the rate was comfortable for them. If the rate was too fast, ten breaths per minute is tested and if too slow, twelve breaths per minute is tested. This paced breathing practice not only assesses the breathing rate, but familiarizes the subject with paced breathing. This test is repeated as many times as necessary, until the subject is comfortable breathing in accordance with the pacer.

The respiration of each subject is recorded during the olfactory experiments. This data was tested to determine if the subjects did indeed pace their breathing accordingly. To do this the correlation coefficient was taken between the frequency spectrum of the pacer and the respiration trace. This analysis was done in the frequency domain instead of the time domain because of the variability of the amplitude of the respiration trace. Although the subjects breathed on pace, their depth of breath varied, this drove down the level of temporal correlation between the two. To account for this, the correlations were done in the frequency domain.

6.4 Odor Detection Practice

This practice session was used to familiarize the subject with the presentation of odors via the cannula. While still fitted with the cannula, the LabView program Main_odor_presentation_program is run to present odors to the subject. This is the same program used during fMRI scanning, its main features will be presented in Section 6.7 and the program is in Appendix D.10. An odor that is not used in the main part of this experiment is repeatedly presented to the subject while the subject breathes at the paced rate. This practice session is also used to ensure that the subject does not breathe
in sniffs during odor presentation. The aim is for the subjects to breathe at a constant rate throughout the experiment. This practice session is also used to train the subject to respond when an odor is presented. At the end of this practice session the cannula is removed.

6.5 Functional Scanning Setup

Before the subject enters the magnet room, the equipment was brought into the room and set up. This limited the time the subject is unnecessarily in the magnetic field. Before entry to the MR room, the subject is instructed to use the restroom and to remove all metallic objects from their body and clothing.

In the MR room were placed the laptop computer, which controlled the olfactometer, collected behavioral response data and collected respiration data, the olfactometer and the LCD projector for display of the breathing pacer and visual stimuli to the subject. All equipment was placed behind the five Gauss line, being behind the five Gauss line limited the interference between the computer and the magnetic field of the MRI. Although all equipment being outside the magnet room is ideal, it was not possible within the scanning environment used. The interference between the equipment was also minimized by encasing all electronics in rf shielded boxes and using shielded cables.

The olfactometer was plugged into a surge protected power supply and to the computer via a 24 bit digital input/output data acquisition card (National Instruments Corporation product: DAQCard-DIO-24). The respiration transducer, which runs on batteries, was turned on and its data out port was plugged into the Mini-Lab data acquisition device as described above. The trigger cable from the MRI was also connected to the Mini-Lab, which was connected to the computer via the USB port. Into the second USB port was a Lumni Touch fiber optic response pad. This needed to be fiber optic, versus metallic, because it crossed the 5 Gauss line and went to the subject. The computer was also connected to the VGA projector which acted as an extension, or second screen, from the computer.
Connected to the olfactometer, via Teflon tubing, was a manifold attached to which were the odor capsules and valves. This manifold contained all the odors in liquid form and each odor capsule was connected to its own solenoid air valve in the olfactometer on one end. This manifold can be seen attached to the head coil in Figure 6.3. The other end,

![Figure 6.3](image.png)

**Figure 6.3** Picture showing a subject in the MRI and the manifold containing the odors.

the output, of the odor capsule flowed into the manifold. The manifold had one input for each odor capsule, one input for clear air and a single output which was connected to the subject's cannula. The olfactometer had control over the presentation of each individual odor and over clear air presentation.

The manifold, odor capsules, and valves were all connected to the head coil of the magnet that surrounded the subject's head while in the magnet. The head coil made a convenient anchor for the assembly that did not interfere with the subject's comfort and easily fit inside the magnet bore.

Once in the room and seated on the magnet's gurney the subject was given ear plugs and fitted with a cannula in their nostrils. Lying supine on the gurney, the subject was
positioned so they were comfortable and their head was aligned correctly. The optimal head alignment was one where the subject’s Anterior Commisure-Posterior Commisure (AC-PC) line was perpendicular to the magnet’s bore direction, an up-down alignment. This was approximated by positioning the nose directly above the ear canal.

Placed over the subject’s head was the head coil which transmitted the rf pulses and received the radiated energy. Attached to the head coil was an adjustable mirror above the subjects’ eyes. This allowed the subject to view the back-projection screen which was placed at their feet. The subject was provided with the Lumni Touch response button box in their right hand. This response button box was used to record when the subject detected an odorant.

Figure 6.4 Drawing of the MR room showing the subject setup.

A single LabView program was used for the odor presentation and behavioral response collection in which the experimenter started the program running before the experiment began. The MR technician started the magnet scanning which sent a TTL pulse through a
coaxial cable. This cable was connected to the Mini-Lab Data Acquisition device. Once the first pulse was received at the computer, the program knew the scan had started and began the experimental stimulation.

The experiment consisted of five odor presentations each lasting twelve seconds and alternated with thirty seconds of clear air. To trigger an odor presentation, the computer sent a digital packet of information to a 24 bit digital input/output data acquisition card (National Instruments Corporation product: DAQCard-DIO-24). This information was decoded by the olfactometer to open or close the solenoids.

6.6 Olfactometer Construction

The design of the olfactometer was based on the model created by Dr. Tyler Lorig at Washington and Lee University [50]. The basic idea was that the olfactometer is a series of computer controlled Teflon solenoid valves. The solenoids switch the air that flows through the tubing to the subject from being clear room air to any of the twelve odors. The bank of solenoids and their switching relays were housed in an rf shielded box and kept behind the MRI's 5 Gauss line. Thirteen Teflon tubes exited the olfactometer and went to the subject in the magnet. These was one for each odor, and one for clear air. The thirteen tubes converged on a Teflon manifold which was mounted to the head coil of the magnet. The manifold contained one odor cylinder per odor. The cylinders each contained one way vales, and a piece of filter paper onto which the liquid odorant was applied. Once closed, the liquid odorant vaporized to fill the chamber. When air was passed through the cylinder the valve opened allowing the odorant to pass to the subjects' nostrils via the cannula.

6.7 Odor Presentation Program

The main program used during the functional MRI scanning and for the pre-scanning odor detection practice, Main_odor_presentation_program as found in Appendix D.10, is described here. Like the program used in the paced breathing practice, this program used
two display screens, one for display to the subject, and one for the experimenter. The display for the subject showed a filling tank used for paced breathing and had an option for biofeedback, which was not used in these experiments. The breathing pacer had a control where the experimenter entered the breathing rate as determined during the practice session.

The breathing pacer was designed so that the odor was maximally inhaled during its presentation. To ensure this, the subject's breathing was set so that they were inhaling at the start of the odor presentation. With this control, odorants were received by the subjects at the very start of the presentation. This would not be the case if the subject were exhaling at the time of odor presentation. To implement this, the actual breathing pacer and phase were adjusted from their imputed settings. The time between odor presentations was determined. This was the length of a single odor presentation period, 12 seconds as used in this experiment, plus the time of clear air presentation, 30 seconds as used here, between odor presentations. The breathing rate was adjusted so that an integer number of breaths were taken during this time. This ensured that the subject was in the same breathing phase at the start of each odor presentation. To ensure that the subject was in the desired breathing phase at the start of the odor presentation, the phase of the pacer was adjusted. The time before the first odor presentation was divided by the breathing rate, the distance the result was from the nearest integer times $2\pi$ was the phase shift required. The result of these manipulations was that odor presentation and inhalation occurred in sync.

The display for the experimenter was much more complicated, giving feedback on the performance of the subject and experimental controls. The program was first triggered to start when it received a TTL pulse from the magnet. The TTL pulse from the magnet is a pulse sent out by the console at the start of every image acquisition, every three seconds in this case. This allowed the LabView program to wait for the magnet to start before stimulus presentation started thereby ensuring accurate experimental timing.

The program recorded subject's breathing, which were displayed on the experimenter's screen, and saved to a text file at completion of the experiment. The breathing was stored
for potential future analysis; however, not used in this experiment. The display of subject’s breathing also allowed the experimenter to see if the subject was properly pacing their breathing. This was imperative because of the odor sampling as previously discussed.

The program allowed input for odor selection and experimental timings. As the olfactometer had twelve channels, twelve different odors were presentable. From the experimenter control panel, the odors were selected along with the timings. To record subject responses, they had in their hand the Lumni touch button response. When the subject pressed a button, the response showed on the screen and the experimenter knew immediately whether the subject detected an odorant.

6.8 Post-scanning Odor Assessment

At the end of the fMRI scanning session the subject is assisted out of the scanner and to a nearby room. There they are seated and again hooked up with the dual-cannula. This post-scanning procedure was used to assess the subjects’ responses to the odors and used a program different from the one used during the scanning session.

The program used here is assess_odor.vi and is found in Appendix D.11. This program incorporated odor presentation, temporal intensity responses, reaction time, reaction duration and a list of behavioral assessment scales. Once the program was started, the subject was presented with a slider on the computer screen. This slider was a digitized version of perceived intensity done with a linear potentiometer [51]. This slider was used by the subject to continually rate the perceived intensity of the odor. The slider being all the way to left was deemed “no perceived odor” and all the way to the right was deemed “maximal perceived odor.” There was a twelve second delay between the presentation of the slider and the odor start. After the odor was turned off the slider remained for an additional twelve seconds.

The time before the odor presentation was used so that the odor detection time was accurate and that the subject did not associate the visual cue with odor presentation start.
The delay after the odor end was used to determine whether there was perceived odor after the end of its presentation. After the end of this odor presentation period, a vertical odor intensity scale was presented to the subjects. This was an analog log scale ranging from “no odor” to “strongest imaginable odor.” Following, was a horizontal seven point odor pleasantness scale. This scale ranged from “extremely unpleasant” on the left to “extremely pleasant” on the right. This procedure repeated for all odorants presented to the subject during the fMRI scanning session.

6.9 Visual Stimulus

Two visual stimuli experiments were performed during this experiment. These both used the same stimulus program which only differed in timing. This program was the standard_flicker program and is found in Appendix D. The program was again broken up into a subject viewing screen and an experimenter screen. On the subject viewing screen the subject always saw a red fixation cross at the center of the screen. During resting periods this cross was in the center of a blank gray screen. During stimulation the screen was filled with black and white squares which reverse at a rate of 8 Hertz. This program was started by either a TTL pulse or a manual button press as in the odor presentation program. The experimenter entered the timings for the experiment and the contrasts between the black and white squares. The experimenter screen, had the added feature of two graphs. These showed the stimulus/rest timings of the overall experiment and the progress of the experiment. This feature provided easy feedback as to the progress of the experiment.

6.10 Odorant Stimuli

Ten different odorants were administered in this experiment. This resulted in each odor being presented twice. The odorants were presented in a pseudorandom order ensuring that the same odor was not presented twice in the same session. The ten odors were: cherry, rootbeer, peppermint, pine, orange, strawberry, clove, lemon, menthol, and lilac.
6.11 Data Acquisition

All scanning occurred at the Hatch Center for MR Research in the Neurological Institute at Columbia University on a Philips Medical Systems Intera 1.5 Tesla Research machine equipped with echo planar capabilities. The functional image acquisitions used a standard EPI gradient echo sequence (TR=3000, TE=50, flip=90, slice thickness 5 mm with no gap, 32 slices with an orientation angle of 30 degrees to the AC-PC line, 20x20 cm FOV, 64x64 matrix) [52]. Fast spin echo T2 and T1 weighted images were acquired for subsequent co-registration of the fMRI data, allowing for better anatomical localization. Each session consisted of the collection of 82 images with the first two being discarded to account for tissue magnetization. This left 80 images or 4 minutes worth of data for each session. All ten subjects engaged in four sessions of odorant stimulation. Nine subjects engaged in one transient and at least one sustained visual stimulation session. Seven subjects engaged in two sessions of the sustained visual stimulus.

6.12 Image Preprocessing Analyses

All processing of imaging data at the individual subject level in this work was performed using FEAT (FMRI Expert Analysis Tool) Version 5.4, part of the FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first two images of each time series were removed from analyses to account for saturation effects leaving 80 total images per time series. Images were corrected for motion using MCFLIRT [53]; non-brain removal using BET (brain extraction tool) [54]; and spatially smoothed with a Gaussian kernal having a full width at half maximum (FWHM) of 8 millimeters. The image intensity of all volumes in the time series were normalized to the mean of the series, high pass temporally filtered at a frequency of 0.044 Hertz and corrected for local autocorrelation [55]. Images were registered to subject specific high resolution images and spatially normalized into standard Talairach space [56] [53][57]. This is a neuroimaging standard that allows comparison of results between different experiments by transforming all results into a metric space.
Group-level analysis was carried out using FLAME (FMRIB’s Local Analysis of Mixed Effects) [58] [59]. Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance of $p=0.05$ [60].

### 6.13 Region of Interest Mask

Regions of interest were automatically generated from the Talairach Deamon [61][57] using the WFUPickAtlas program[62]. This program provided an easy interface to the Talairach atlas and the AAL atlas[63]. Using this program ROIs were generated for the following regions: Brodmann Area (BA) 17, BA18, amygdala, anterior cingulate, Calcarine fissure, entorhinal, frontal inferior orbit, frontal middle orbit, frontal superior orbit, fusiform, hippocampus, insula, middle cingulate, olfactory, the union of frontal orbit and BA47 [64], parahippocampus, piriform, posterior cingulate, temporal pole and thalamus. These regions were chosen based on the literature as being involved in olfactory or visual stimuli processing. Each ROI overlaid on an anatomical image are found in Appendix C.
CHAPTER 7
RESULTS

7.1 Behavioral Results

All subjects were tested before fMRI scanning for their perceived abilities to identify and detect odorants. The two scales had seven points ranging from “Totally Unable To Sense Smells” (value 1) to “Exceptional (Very Superior)” (value 7). Both had “Normal (Good)” as a middle point (value 4). The mean and standard errors for the scales were 4.6 (0.11) for the odor identification with a range of 3 to 6 and 4.9 (0.11) for the odor detection with a range of 4 to 7.

Subjects also were tested for their odorant thresholds. This test starts off with a zero concentration of odorant and increases the concentration until subjects reliably detect the odorant. Therefore, a lower value on this scale corresponds to detection of odorant at lower concentrations. Eight subjects were given this test and the mean value (standard error) was 6.93 (0.32) with a range of 2.75 to 11.25.

The results of analyzing the respiration data from the olfactory experiment showed good agreement between the pacer and the actual respiration. Data from eight of the ten subjects for each run had mean correlations (and standard errors) of 0.934 (0.0037), 0.91 (0.0049), 0.89 (0.0063), and 0.91 (0.0062).

To determine if the subjects actually detected the odorants, they were instructed to press a button in their right hand upon odorant detection. The mean percentage of odorant detection (and standard error) for each run was 97.5 (0.88), 97.5 (0.88), 100 (0), and 97.5 (0.88).
7.2 Visual Data

7.2.1 GLM Results from Sustained Stimulus

Group analysis of the sustained, 12 second, visual stimulus data showed widespread task related signal change throughout Brodmann areas 17 and 18, the calcarine fissure and the fusiform. Signal change was also detected in the hippocampus and thalamus. Figure 7.1 shows a composite image displaying these results and Table 7.1 summarizes them in the ROIs.

Figure 7.1 Results for sustained visual stimulus in axial orientation overlaid on the group mean of all anatomical images, for seven subjects, 2 runs per subject.
Table 7.1 ROI Results for Sustained Visual Stimulus

<table>
<thead>
<tr>
<th>ROI</th>
<th>% ROI &gt; threshold (R/L)</th>
<th>Mean Z-score (R/L)</th>
<th>Max Z-Score (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA 17</td>
<td>64.16/89.71</td>
<td>3.07/3.28</td>
<td>3.95/4.02</td>
</tr>
<tr>
<td>BA 18</td>
<td>57.94/66.48</td>
<td>3.08/3.02</td>
<td>4.26/4.02</td>
</tr>
<tr>
<td>amygdala</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>calcarine</td>
<td>54.49/46.83</td>
<td>3.18/3.17</td>
<td>4.26/4.10</td>
</tr>
<tr>
<td>entorhinal</td>
<td>0/3.02</td>
<td>0/2.46</td>
<td>0/2.62</td>
</tr>
<tr>
<td>frontal inf. orbital</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>frontal mid. orbital</td>
<td>0.07/0</td>
<td>2.31/0</td>
<td>2.31/0</td>
</tr>
<tr>
<td>frontal sup. orbital</td>
<td>0.06/0</td>
<td>2.30/0</td>
<td>2.30/0</td>
</tr>
<tr>
<td>fusiform</td>
<td>33.24/36.97</td>
<td>2.80/2.99</td>
<td>3.67/3.87</td>
</tr>
<tr>
<td>hippocampus</td>
<td>7.72/3.24</td>
<td>2.89/2.62</td>
<td>3.74/3.04</td>
</tr>
<tr>
<td>insula</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>mid. cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>olfactory</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>orbital frontal/BA 47</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>0.44/0</td>
<td>2.41/0</td>
<td>2.67/0</td>
</tr>
<tr>
<td>piriform</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>post. cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>sup. temporal pole</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>thalamus</td>
<td>2.92/0.87</td>
<td>2.80/2.58</td>
<td>3.74/3.05</td>
</tr>
</tbody>
</table>
7.2.2 GLM Results from Transient Stimulus

Group analysis of the transient, 2 second, visual stimulus data showed widespread task related signal change throughout Brodmann areas 17 and 18, the Calcarine fissure and the fusiform, as in the sustained stimulus. Unlike the sustained stimulus, task related signal change was not shown in the hippocampus or thalamus. It is also worth noting that although signal change was found in similar regions for the two tasks, their extents differ. These results are displayed in Figure 7.2 and summarized within the ROIs in Table 7.2.

Figure 7.2 Results for transient visual stimulus in axial orientation overlaid on the group mean of all anatomical images, for nine subjects, 1 run per subject.
Table 7.2 ROI Results for Transient Visual Stimulus

<table>
<thead>
<tr>
<th>ROI</th>
<th>% ROI &gt; threshold (R/L)</th>
<th>Mean Z-score (R/L)</th>
<th>Max Z-Score (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA 17</td>
<td>53.61/67.94</td>
<td>3.22/3.37</td>
<td>4.11/4.17</td>
</tr>
<tr>
<td>BA 18</td>
<td>56.45/55.03</td>
<td>3.17/3.16</td>
<td>4.25/4.30</td>
</tr>
<tr>
<td>amygdala</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>calcarine</td>
<td>48.37/49.46</td>
<td>3.23/3.16</td>
<td>4.16/4.10</td>
</tr>
<tr>
<td>entorhinal</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>frontal inf. orbital</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>frontal mid. orbital</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>frontal sup. orbital</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>fusiform</td>
<td>31.71/32.02</td>
<td>2.92/3.14</td>
<td>3.92/4.05</td>
</tr>
<tr>
<td>hippocampus</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>insula</td>
<td>1.64/0</td>
<td>2.50/0</td>
<td>2.84/0</td>
</tr>
<tr>
<td>mid. cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>olfactory</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>orbital frontal/BA 47</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>0.06/0.35</td>
<td>2.35/2.49</td>
<td>2.35/2.71</td>
</tr>
<tr>
<td>piriform</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>post. cingulate</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>sup. temporal pole</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>thalamus</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>
7.2.3 Extracted Responses from Sustained and Transient Stimuli

Data from the visual experiments shown in the previous section were analyzed within ROIs. From each ROI, a mean time course vector was created. From this mean vector, the Kalman filter was applied to extract the underlying response to the stimuli. The extracted responses were averaged across subjects and are shown with their standard errors. The results are shown for each ROI for the sustained stimulus and the transient stimulus in Figures 7.3 and 7.4. All graphs have y-axes of percent signal change. Note that the range for BA 17, 18 and Calcarine fissure are -0.5 to 1.5%, and for all others, the range is -0.25 to 0.6%. The varying ranges is to compensate for the robust signal change in the visual areas and to show more detail in the areas showing less signal change. From inspection of the extracted responses in Brodmann areas 17 and 18 and the Calcarine fissure there is clearly a differential extracted response. Although the Z-scores within these regions were comparable (see Tables 7.1 and 7.2) the percent signal changes differed.

![Figure 7.3](image)

**Figure 7.3** Extracted HRF’s in response to sustained and transient visual stimuli. Note that vertical axis limits all range from -0.25 to 0.5 percent signal change except for BA17 and BA18 which range from -0.5 to 1.5.
From these extracted responses, the width of the response was measured. This calculation was taken as the full width of the response at half the maximal value (FWHM). All responses were evaluated in this way; therefore, the FWHM should be interpreted in those regions showing task related signal change. The FWHM values were calculated for every subject and then averaged across subjects. These results along with standard errors are plotted in Figure 7.5 and shown in Table 7.3. T tests within the ROIs and across stimuli shows the following significant differences: left BA17 $T=4.8286$, $p=0.0019$; right BA17 $T=2.47$, $p=0.043$; left BA18 $T=3.06$, $p=0.022$; right BA18 $T=2.96$, $p=0.025$; and right Calcarine fissure $T=4.73$, $p=0.0032$. 

**Figure 7.4** Extracted HRF’s in response to sustained and transient visual stimuli, a continuation of Figure 7.3.
Figure 7.5  Mean of the estimated widths of the responses as shown in Figures 7.4. Values determined as the full width at half the maximum value shown along with the standard error of the mean.
Table 7.3 Estimated Widths of Responses to Visual Data

<table>
<thead>
<tr>
<th>ROI</th>
<th>Mean FWHM (Stand. Err.)</th>
<th>Mean FWHM (Stand. Err.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained Stimulus (R/L)</td>
<td>Trained Stimulus (R/L)</td>
</tr>
<tr>
<td>BA17</td>
<td>11.86(1.81) / 12.16(1.81)</td>
<td>8.36(4.45) / 6.56(2.28)</td>
</tr>
<tr>
<td>BA18</td>
<td>13.13(2.69) / 13.36(2.61)</td>
<td>8.44(4.27) / 9.12(4.66)</td>
</tr>
<tr>
<td>amygdala</td>
<td>9.14(7.22) / 5.39(2.09)</td>
<td>13.64(5.21) / 9.29(5.74)</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>8.77(4.11) / 7.12(3.39)</td>
<td>6.84(2.44) / 7.97(4.17)</td>
</tr>
<tr>
<td>calcarine</td>
<td>12.26(3.64) / 13.19(1.52)</td>
<td>6.76(3.59) / 9.89(6.7)</td>
</tr>
<tr>
<td>entorhinal</td>
<td>8.99(4.66) / 8.00(6.84)</td>
<td>10.72(8.43) / 7.79(3.74)</td>
</tr>
<tr>
<td>frontal inferior orbit</td>
<td>6.99(4.35) / 9.69(2.44)</td>
<td>7.79(3.95) / 8.92(5.65)</td>
</tr>
<tr>
<td>frontal middle orbit</td>
<td>8.87(4.18) / 13.31(12.01)</td>
<td>4.09(0.91) / 15.29(17.66)</td>
</tr>
<tr>
<td>frontal superior orbit</td>
<td>11.35(11.46) / 10.19(7.31)</td>
<td>9.6735(5.74) / 11.99(5.40)</td>
</tr>
<tr>
<td>fusiform</td>
<td>12.12(4.03) / 11.59(4.08)</td>
<td>10.13(5.11) / 10.25(5.30)</td>
</tr>
<tr>
<td>hippocampus</td>
<td>10.04(4.92) / 10.59(7.25)</td>
<td>16.34(1.51) / 9.59(6.04)</td>
</tr>
<tr>
<td>insula</td>
<td>10.09(10.73) / 2.99(0)</td>
<td>7.79(4.35) / 8.21(4.10)</td>
</tr>
<tr>
<td>middle cingulate</td>
<td>5.99(0.59) / 8.77(7.95)</td>
<td>15.05(8.80) / 11.32(4.73)</td>
</tr>
<tr>
<td>olfactory</td>
<td>6.19(2.51) / 7.37(3.20)</td>
<td>7.74(5.59) / 7.49(4.43)</td>
</tr>
<tr>
<td>frontal orbit/BA47</td>
<td>5.89(3.41) / 7.19(3.33)</td>
<td>9.79(5.23) / 6.52(1.07)</td>
</tr>
<tr>
<td>parahippocampus</td>
<td>11.09(6.78) / 4.79(0.60)</td>
<td>12.59(6.57) / 10.94(8.01)</td>
</tr>
<tr>
<td>piriform</td>
<td>5.24(4.02) / 6.44(1.48)</td>
<td>6.79(3.51) / 10.43(6.32)</td>
</tr>
<tr>
<td>posterior cingulate</td>
<td>16.19(12.30) / 8.39(0)</td>
<td>6.71(3.61) / 10.61(5.70)</td>
</tr>
<tr>
<td>temporal pole</td>
<td>3.89(2.09) / 21.29(13.50)</td>
<td>11.54(5.72) / 9.35(6.18)</td>
</tr>
<tr>
<td>thalamus</td>
<td>35.09(0) / 13.94(12.51)</td>
<td>8.99(5.22) / 11.77(4.23)</td>
</tr>
</tbody>
</table>
7.3 Olfactory Data

7.3.1 GLM Results from Olfaction Data

Group analysis of the olfaction data from ten subjects each with two sessions of data are shown here. The results show widespread task related signal change in all regions of interest. In particular, there is robust signal change in the bilateral amygdala and piriform. These results are displayed in Figure 7.6 in an axial orientation and in Figure 7.7 in a coronal orientation covering just the frontal regions. The results are also summarized within the ROIs in Table 7.4. This table shows the percentage of each ROI that exceeds the statistical threshold and the mean and maximum Z-scores within each ROI. These results are promising because there is robust task related signal change in the primary olfactory cortex, namely the piriform (percent of ROI above threshold is 88 and 90% R/L) and also the secondary olfactory cortex, namely the inferior frontal orbit (percent of ROI above threshold is 30 and 33% R/L).

Figure 7.6 Results for olfaction group data in axial orientation overlaid on the group mean of all anatomical images.
Figure 7.7  Results for olfaction group data in coronal orientation overlaid on the group mean of all anatomical images.

Table 7.4  ROI Analyses for Olfactory Stimuli

<table>
<thead>
<tr>
<th>ROI</th>
<th>% of ROI &gt; threshold (R/L)</th>
<th>Mean Z-score (R/L)</th>
<th>Max Z-Score (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA 17</td>
<td>13.86/6.32</td>
<td>2.58/2.47</td>
<td>2.87/2.74</td>
</tr>
<tr>
<td>BA 18</td>
<td>7.41/4.14</td>
<td>2.60/2.48</td>
<td>3.03/2.90</td>
</tr>
<tr>
<td>amygdala</td>
<td>96.96/81.10</td>
<td>3.62/3.75</td>
<td>4.79/4.80</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>32.20/20.89</td>
<td>3.13/3.08</td>
<td>4.24/4.12</td>
</tr>
<tr>
<td>calcine</td>
<td>8.28/0.04</td>
<td>2.58/2.31</td>
<td>3.22/2.31</td>
</tr>
<tr>
<td>entorhinal</td>
<td>58.64/38.67</td>
<td>3.13/2.90</td>
<td>4.14/4.21</td>
</tr>
<tr>
<td>frontal inf. orbital</td>
<td>29.59/32.98</td>
<td>2.93/2.93</td>
<td>3.67/3.76</td>
</tr>
<tr>
<td>frontal mid. orbital</td>
<td>10.30/9.87</td>
<td>2.97/2.72</td>
<td>4.07/3.86</td>
</tr>
<tr>
<td>frontal sup. orbital</td>
<td>9.76/19.03</td>
<td>3.11/3.01</td>
<td>4.10/3.86</td>
</tr>
<tr>
<td>fusiform</td>
<td>4.75/9.89</td>
<td>2.54/2.82</td>
<td>2.90/3.66</td>
</tr>
<tr>
<td>hippocampus</td>
<td>24.75/28.64</td>
<td>2.98/3.33</td>
<td>4.37/4.67</td>
</tr>
<tr>
<td>insula</td>
<td>55.70/47.74</td>
<td>3.00/3.12</td>
<td>3.95/4.07</td>
</tr>
<tr>
<td>mid. cingulate</td>
<td>33.77/33.87</td>
<td>3.30/3.31</td>
<td>4.55/4.61</td>
</tr>
<tr>
<td>olfactory</td>
<td>25.24/30.69</td>
<td>3.63/3.45</td>
<td>4.83/4.36</td>
</tr>
<tr>
<td>orbital frontal/BA 47</td>
<td>31.93/38.64</td>
<td>2.90/2.95</td>
<td>3.65/3.69</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>18.65/27.81</td>
<td>2.97/3.10</td>
<td>4.15/4.47</td>
</tr>
<tr>
<td>piriform</td>
<td>88.01/90.46</td>
<td>3.50/3.52</td>
<td>4.74/4.80</td>
</tr>
<tr>
<td>post. cingulate</td>
<td>7.80/4.04</td>
<td>2.54/2.46</td>
<td>2.93/2.73</td>
</tr>
<tr>
<td>sup. temporal pole</td>
<td>25.57/14.20</td>
<td>2.87/2.86</td>
<td>3.82/3.88</td>
</tr>
<tr>
<td>thalamus</td>
<td>19.93/11.59</td>
<td>2.82/2.66</td>
<td>3.41/3.30</td>
</tr>
</tbody>
</table>
7.3.2 Extracted Responses from Olfaction Data

Data from the olfaction experiments shown in the previous section were analyzed with the Kalman filter within the ROIs. The extracted responses from the mean time course of each ROI was found using the Kalman filter. The mean extracted responses across subjects for each ROI are shown in Figures 7.8 and 7.9. All graphs have y-axes of percent signal change. The range for all graphs extend from -0.5% to +0.5%. This is in contrast to the visual, data which had much stronger signal changes in the visual ROIs. Note that the most noticeable responses are in the amygdala, entorhinal and piriform. This fits well with what is expected, since these three regions showed the most robust responses in the GLM analysis. These extracted responses were analyzed to determine their full width at half maximum value for each subject. The mean and standard errors for this analysis are displayed in Figure 7.10 and summarized in Table 7.5.

![Graphs showing extracted HRF's in response to odorant stimuli.](image)

**Figure 7.8** Extracted HRF's in response to odorant stimuli.
Figure 7.9 Extracted HRF’s in response to odorant stimuli.
Figure 7.10  Mean of the estimated widths of the responses as shown in Figures 7.8 and 7.9. Values determined as the full width at half the maximum value shown along with the standard error of the mean.
Table 7.5  Estimated Widths of the Responses to the Olfaction Data

<table>
<thead>
<tr>
<th>ROI</th>
<th>Mean FWHM (Standard Error) (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA17</td>
<td>5.35(0.69) / 5.76(0.72)</td>
</tr>
<tr>
<td>BA18</td>
<td>7.32(2.3678) / 6.12(0.54)</td>
</tr>
<tr>
<td>amygdala</td>
<td>6.34(2.18) / 6.60(2.66)</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>10.50(11.28) / 10.60(12.46)</td>
</tr>
<tr>
<td>calcarine</td>
<td>7.14(3.75) / 7.20(3.28)</td>
</tr>
<tr>
<td>entorhinal</td>
<td>6.84(4.60) / 5.77(2.36)</td>
</tr>
<tr>
<td>frontal inferior orbit</td>
<td>11.83(8.42) / 7.13(4.14)</td>
</tr>
<tr>
<td>frontal middle orbit</td>
<td>5.20(0.76) / 6.90(3.15)</td>
</tr>
<tr>
<td>frontal superior orbit</td>
<td>6.40(2.25) / 7.50(4.52)</td>
</tr>
<tr>
<td>fusiform</td>
<td>8.91(3.86) / 8.45(3.91)</td>
</tr>
<tr>
<td>hippocampus</td>
<td>6.40(1.50) / 8.95(8.42)</td>
</tr>
<tr>
<td>insula</td>
<td>5.95(0.94) / 6.2493(0.93)</td>
</tr>
<tr>
<td>middle cingulate</td>
<td>7.85(2.88) / 6.47(1.97)</td>
</tr>
<tr>
<td>olfactory</td>
<td>5.65(0.99) / 4.45(0.81)</td>
</tr>
<tr>
<td>frontal orbit/BA47</td>
<td>13.02(9.06) / 6.40(2.95)</td>
</tr>
<tr>
<td>parahippocampus</td>
<td>5.40(0.88) / 6.95(3.46)</td>
</tr>
<tr>
<td>piriform</td>
<td>6.82(2.76) / 5.06(0.63)</td>
</tr>
<tr>
<td>posterior cingulate</td>
<td>12.00(9.67) / 11.30(9.50)</td>
</tr>
<tr>
<td>temporal pole</td>
<td>9.20(5.06) / 6.60(3.47)</td>
</tr>
<tr>
<td>thalamus</td>
<td>11.92(10.94) / 5.92(1.99)</td>
</tr>
</tbody>
</table>
7.4 Comparison of Kalman Filter Derived Model and other Statistical Models

This section is devoted to the comparison of Kalman filter results to other models. These models are shown in Figure 7.11. From top to bottom the models are: 1) the stimulus with no convolution, 2) the stimulus model delayed by six seconds, 3) the stimulus model convolved with a single gamma model, 4) the stimulus convolved with the standard double gamma model, 5) a model with a shortened “on” time of six seconds convolved with the double gamma model (this is modeled after the work by Poellinger et al. 2001 [4]), 6) the exponential decaying model based on the work by Sobel et al. 2000 [3] convolved with three finite linear basis functions [40], and 7) the Kalman design (the one shown is just an example, each ROI in each subject had its own Kalman filter derived model). These

![Comparison of models](image)

**Figure 7.11** The seven designs compared for variance accountability. The design shown for Kalman filter analysis is only an example.

models were compared within the sustained stimulus visual data and the olfactory data using analysis of variance to determine which model accounted for the most variance in the data. In particular this tested whether the Kalman filter when trained on one data set could predict the next data set better than *a prior* defined models.
7.4.1 Visual Data

The results from the ANOVA for the visual data comparing all models are shown in Table 7.6. These results show main effects of METHOD and ROI with ROI interacting with METHOD and HEMISPHERE.

**Table 7.6 ANOVA Results for Visual Data from Sustained Stimulus**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>127559</td>
<td>19</td>
<td>6713.63</td>
<td>8.71</td>
<td>0</td>
</tr>
<tr>
<td>Method</td>
<td>8955.2</td>
<td>6</td>
<td>1492.54</td>
<td>7.15</td>
<td>0</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>22.7</td>
<td>1</td>
<td>22.71</td>
<td>0.16</td>
<td>0.7009</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>16168.2</td>
<td>114</td>
<td>140.95</td>
<td>5.81</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Hemisphere</td>
<td>4570</td>
<td>19</td>
<td>240.52</td>
<td>9.92</td>
<td>0</td>
</tr>
<tr>
<td>Method*Hemisphere</td>
<td>30.4</td>
<td>6</td>
<td>5.07</td>
<td>0.21</td>
<td>0.974</td>
</tr>
<tr>
<td>Error</td>
<td>39561.6</td>
<td>1632</td>
<td>24.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>299287.6</td>
<td>1959</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of METHOD is shown in Figure 7.12 and these results were investigated with Scheffé post-hoc tests. Scheffé post-hoc tests with an alpha equal to 0.05

![Main Effect of METHOD Tested on the Second Session](image)

**Figure 7.12** Main Effect of METHOD after first run of visual data and tested on the second run.
showed that the Gamma and the Standard models were the two best at predicting task related signal change in the visual data. Specifically these two were significantly better than the Kalman, Kalman < Gamma $t(279)=-4.641$, $p=5.341\times10^{-06}$, Kalman < Standard $t(279)=-4.837$, $p=2.183\times10^{-06}$. Other results are: FLOBS > Poellinger $t(279)=6.439$, $p=5.225\times10^{-06}$, FLOBS > Stimulus $t(279)=7.490$, $p=9.079\times10^{-013}$, Kalman > Poellinger $t(279)=5.707$, $p=2.934\times10^{-08}$, Kalman > Stimulus $t(279)=7.556$, $p=5.980\times10^{-013}$, Delayed > Poellinger $t(279)=6.784$, $p=7.002\times10^{-11}$, Delayed > Stimulus $t(279)=8.495$, $p=1.110\times10^{-015}$, Gamma > Poellinger $t(279)=8.346$, $p=3.331\times10^{-15}$, Gamma > Stimulus $t(279)=9.1467$, $p=0$, Poellinger < Standard $t(279)=-8.675$, $p=3.486\times10^{-16}$, Poellinger > Stimulus $t(279)=6.801$, $p=6.312\times10^{-11}$, Standard > Stimulus $t(279)=9.151$, $p=0$.

The main effect of ROI is shown in Figures 7.13 and 7.14 and these results were investigated with Scheffé post-hoc tests. Specifically, it is worthwhile to note that the three most significant regions were the three main visual information processing regions, BA 17, BA18 and Calcarine fissure. Scheffeé post-hoc tests with an alpha equal to 0.05 showed

**Figure 7.13** Main Effect of ROI after first run of visual data and tested on the second run.

**Figure 7.14** Main Effect of ROI after first run of visual data and tested on the second run.

that BA17 was significantly different from BA18, amyg, AC, calc, entorhinal, f inf orb, f mid orb, f sup orb, fus, hipp, ins, mid cing, olf, f orb/BA47, parahipp, piriform, post cing, temp pole and thal. And that the calcarine is significantly different from BA17, amyg, AC,
entorhinal, f inf orb, f mid orb, f sup orb, fus, hipp, ins, mid cing, olf, f orb/BA47, parahipp, piriform, post cing, temp pole and thal. And that BA18 was significantly different from BA17, amyg, AC, entorhinal, f inf orb, f mid orb, f sup orb, fus, hipp, ins, mid cing, olf, f orb/BA47, parahipp, piriform, post cing, temp pole and thal.

### 7.4.2 Olfaction Data

The results from the ANOVA for the olfactory data comparing all models are shown in Table 7.7. These results showed a main effect of ROI and METHOD and ROI interacting with HEMISPHERE.

**Table 7.7** ANOVA Results from One Run of Data Tested the Second

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>108936.2</td>
<td>19</td>
<td>5733.5</td>
<td>17.63</td>
<td>0</td>
</tr>
<tr>
<td>Method</td>
<td>834.5</td>
<td>6</td>
<td>139.1</td>
<td>0.48</td>
<td>0.8109</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>601.2</td>
<td>1</td>
<td>601.2</td>
<td>0.04</td>
<td>0.8364</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>2189.8</td>
<td>114</td>
<td>19.2</td>
<td>0.47</td>
<td>1</td>
</tr>
<tr>
<td>ROI*Hemisphere</td>
<td>5301.6</td>
<td>19</td>
<td>279</td>
<td>6.87</td>
<td>0</td>
</tr>
<tr>
<td>Method*Hemisphere</td>
<td>9.4</td>
<td>6</td>
<td>1.6</td>
<td>0.04</td>
<td>0.9998</td>
</tr>
<tr>
<td>Error</td>
<td>97182.6</td>
<td>2391</td>
<td>40.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>613087.2</td>
<td>2799</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is no main effect of METHOD; however, the percent variance accounted for across models are shown in Figure 7.15. This plot was included to show the three best models were the Poellinger, FLOBS and the Kalman models.

The significant main effect of ROI is shown in Figures 7.16 and 7.17 and these results were investigated using Scheffé post-hoc tests. These results showed that the three main regions involved in the processing of odorant information are the piriform, the amygdala and the insula, three regions comprising the primary olfactory cortex. Scheffé post-hoc tests with an alpha of 0.05 showed that piriform was significantly different from BA17, BA18, AC, calc, f inf orb, f sup orb, fus, mid cing, f orb/BA47 and post cing. The amygdala was significantly different from BA17, BA18, AC, f inf orb, fus, mid cing, f orb/BA47 and post cing. And that the insula was significantly different from BA18 and post cing.
**Figure 7.15** Non-significant main effect of METHOD after one session of training, and tested on the second session.

**Figure 7.16** Main Effect of ROI after one session of training, and tested on the second session.

**Figure 7.17** Main Effect of ROI after one run of training, and tested on the second run.
7.4.3 Predicting the Opposite Hemisphere

The overall aim of this work was to extract time varying behavior from fMRI data, which was tested in the Specific Aim 3. If this hypothesis were true, than using one hemisphere for the prediction of the next is confounded by the effect of interest. To circumvent this confound, data was trained on one hemisphere and tested on the opposite hemisphere. This only made the assumption that any time varying effects were common across hemispheres.

In these analyses the models were all trained on one hemisphere and the estimated responses were used as predictors of the opposite hemisphere. The same seven models were used, and were compared again, using analysis of variance with the dependent measure being the percentage of variance accounted for.

7.4.4 Olfaction Data from Session One

Using the Left Hemisphere to Predict the Right in Session One

The ANOVA results for olfactory data, session one, training on the data from the left hemisphere and testing on data from the right, are shown in Table 7.8.

Table 7.8 ANOVA Results for Olfaction Data, Session One, Left Hemisphere Predicting Right

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI Method</td>
<td>3542.8</td>
<td>19</td>
<td>186.46</td>
<td>1.68</td>
<td>0.0445</td>
</tr>
<tr>
<td></td>
<td>12104.4</td>
<td>6</td>
<td>2017.41</td>
<td>8.97</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>2547.6</td>
<td>114</td>
<td>22.35</td>
<td>1.5</td>
<td>0.0009</td>
</tr>
<tr>
<td>Error Total</td>
<td>15244.6</td>
<td>1026</td>
<td>14.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>107576.5</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interestingly, there was a main effect of method. This contrasts the cross session prediction results in Section 7.4.2. The main effect of method is shown in Figure 7.18 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 showed that the FLOBS and Kalman method do not significantly differ from each other but accounted for a significantly greater percentage of the variance in the data than all other methods. The method accounting for the third greatest percentage of
variance was the Poellinger method which was an informed design based on other olfactory research [4].

**Main Effect of METHOD for Prediction of Right Hemisphere**

<table>
<thead>
<tr>
<th>METHOD</th>
<th>Percent Variance Explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus</td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td></td>
</tr>
<tr>
<td>Poellinger</td>
<td></td>
</tr>
<tr>
<td>FLOBS</td>
<td></td>
</tr>
<tr>
<td>Kalman</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 7.18** Significant main effect of METHOD trained on the left hemisphere to predict the right in session one.

The main effect of ROI is shown in Figures 7.19 and 7.20 and these results were investigated using Scheffé post-hoc tests. The Scheffé post-hoc tests showed the left hemisphere regions that predicted their contra-lateral hemispheres significantly better than other regions at a threshold of alpha equal to 0.05. BA18 was significantly different from AC, f mid orb, f sup orb and olf. The amygdala was significantly different from f mid orb, f sup orb and olf. The hippocampus was significantly different from f mid orb, f sup orb and olf.
Figure 7.19  Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one.

Figure 7.20  Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one.
Using the Right Hemisphere to Predict the Left in Session One

The ANOVA results for olfactory data, session one, training on the data from the right hemisphere and testing on data from the left, are shown in Table 7.9.

Table 7.9 ANOVA Results for Olfaction Data, Session One, Right Hemisphere Predicting Left

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>5798.4</td>
<td>19</td>
<td>305.18</td>
<td>2.68</td>
<td>0.0004</td>
</tr>
<tr>
<td>Method</td>
<td>12113.2</td>
<td>6</td>
<td>2018.86</td>
<td>8.42</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>2793.6</td>
<td>114</td>
<td>24.51</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>13245.7</td>
<td>1026</td>
<td>12.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>101116.6</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure 7.21 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 showed that the FLOBS and Kalman method did not significantly differ from each other but accounted for a significantly greater percentage of the variance in the data than all other methods.

Figure 7.21 Significant main effect of METHOD trained on the right hemisphere to predict the left in session one.
The main effect of ROI is shown in Figures 7.22 and 7.23 and these results were investigated using Scheffé post-hoc tests. The Scheffé post-hoc tests showed the right hemisphere regions that predicted their contra-lateral hemispheres significantly better than other regions at a threshold of alpha equal to 0.05. The fusiform was significantly different from BA17, AC, f inf orb, f mid orb, f sup orb, olf, f orb/BA47, parahipp, post cing, and temp pole. The amygdala was significantly different from BA17, f inf orb, f mid orb, f sup orb, olf, f orb/BA47, parahipp, and temp pole. The hippocampus was significantly different from BA17, f inf orb, f mid orb, f sup orb, olf and f orb/BA47.

**Figure 7.22** Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one.

**Figure 7.23** Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one.
7.4.5 Olfaction Data for Subsequent Sessions

All four sessions of olfactory data were investigated for cross hemisphere predictability. These results are shown in their entirety in Section B.1. The interesting result from the subsequent data sessions, is that the main effect of method is significant for all three sessions; however, the Kalman filter derived model was significantly better at predicting task related signal change across the hemispheres. These results are shown here for convenience for session two in Figures 7.24 and 7.25, for session three in Figures B.7 and 7.27 and for session four in Figures 7.28 and 7.29.

**Figure 7.24** Significant main effect of METHOD trained on the left hemisphere to predict the right in session two.

**Figure 7.25** Significant main effect of METHOD trained on the right hemisphere to predict the left in session two.
Figure 7.26  Significant main effect of METHOD trained on the left hemisphere to predict the right in session three.

Figure 7.27  Significant main effect of METHOD trained on the right hemisphere to predict the left in session three.

Figure 7.28  Significant main effect of METHOD trained on the left hemisphere to predict the right in session four.

Figure 7.29  Significant main effect of METHOD trained on the right hemisphere to predict the left in session four.
7.5 Extraction of Time Dependent Changes

Using an exponentially decaying model, like that used in Sobel et al. 2000 [3], the decay rate was tested. This model was chosen for its precedence in the literature for olfactory studies and for being parsimonious. Once the Kalman filter was fit to the data, the peak amplitudes at every time point were extracted for the entire experiment. The aim here was to test whether the measured signal from certain regions of the brain habituate at rates different from other regions. Once the model was fit for every subject and across ROI and HEMISPHERE the results were entered into an ANOVA model. This model had exponential decay/growth rate as a dependent variable and two factors. These factors were ROI with 20 levels and HEMISPHERE with two levels. The results from this analysis are shown in Table 7.10.

Table 7.10 ANOVA Results for Exponential Habituation Rate

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>2.4815e-005</td>
<td>19</td>
<td>1.3604e-006</td>
<td>2.06</td>
<td>0.0082</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>5.4594e-007</td>
<td>1</td>
<td>5.4594e-007</td>
<td>1.33</td>
<td>0.2779</td>
</tr>
<tr>
<td>ROI*Hemisphere</td>
<td>6.0256e-006</td>
<td>19</td>
<td>3.1714e-007</td>
<td>1.29</td>
<td>0.1976</td>
</tr>
<tr>
<td>Error</td>
<td>4.2147e-005</td>
<td>171</td>
<td>2.4648e-007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.0658e-004</td>
<td>399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These results showed a main effect of ROI, Figures 7.30 and 7.31 show this effect. Scheffé post-hoc tests with an alpha equal to 0.05 showed that the olfactory ROI had a decay rate significantly faster than that of all other ROI.

Plots of the data, the Kalman filter estimate and the exponential model fit show the decaying effect within the olfactory ROI. Figure 7.32 shows this decaying effect in the left olfactory ROI. Note that the first initial red estimate spike is an effect of training of the filter, and was not used in the exponential model fit. This plot includes data from four runs of data, the entire experiment concatenated. Figure 7.33 shows this plot broken up into the four separate scanning sessions. It is clearly shown that the amplitude of the response to each odorant is maximal in the first session, but decreasing. This decrease occurred across
Figure 7.30 Main effect of ROI for exponential habituation rate.

Figure 7.31 Main effect of ROI for exponential habituation rate.

the first and second sessions with the third and fourth appearing stabilized. Figures 7.34 and 7.35 show the same effects in the right olfactory ROI as described above.
Figure 7.32  Time plot of data from the left olfactory ROI, the Kalman estimate of the data and the exponential fit to the peaks of each odor response.

Figure 7.33  Time plot of data from the left olfactory ROI and the Kalman estimate split over the four sessions of data. A: session 1, B: session 2, C: session 3 and D: session 4
Figure 7.34  Time plot of data from the left olfactory ROI, the Kalman estimate of the data and the exponential fit to the peaks of each odor response.

Figure 7.35  Time plot of data from the right olfactory ROI and the Kalman estimate split over the four sessions of data. A: session 1, B: session 2, C: session 3 and D: session 4
The real advantage of the Kalman filter is to extract a signal response over time. Figures 7.36 and 7.37, which follow, demonstrate this. These are surface plots which show the extracted response over experimental time and over each individual response. The axes of the graphs are therefore 0 to 960 seconds for the experimental time progression, 0 to 39 seconds for signal response progression and percent signal change for the vertical axis. Although a model was only fit to the changing amplitude these plots allow models to be fit to any number of signal response characteristic. These could include latency, spread or undershoot. The unique characteristic of the Kalman filter is that these characteristics are tractable over experimental time.

Figure 7.36 Surface graph of extracted response over time in left olfactory ROI.
Figure 7.37  Surface graph of extracted response over time in right olfactory ROI.
7.5.1 Inclusion of Estimated Decay Terms into Model Comparisons

After extraction and analysis of the exponential fit, the results were used to create an eighth model. This new model is the Kalman filter model multiplied by the estimated exponential term found in Session 7.5. The results for session two are in Appendix B. The results for session two are in Appendix B.

Using the Left Hemisphere to Predict the Right  The ANOVA results for olfactory data, session one, training on the data from the left hemisphere and testing on data from the right, and shown in Table 7.11. These results show a main effect of METHOD,

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>4835.7</td>
<td>19</td>
<td>254.51</td>
<td>1.8</td>
<td>0.0266</td>
</tr>
<tr>
<td>Method</td>
<td>14462.4</td>
<td>7</td>
<td>2066.05</td>
<td>9.93</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>3256.5</td>
<td>133</td>
<td>24.48</td>
<td>1.48</td>
<td>0.0006</td>
</tr>
<tr>
<td>Error</td>
<td>19755.8</td>
<td>1197</td>
<td>16.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>131535.8</td>
<td>1599</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

see Figure 7.38. When investigated with Scheffé post-hoc tests, these results showed no significant difference between the FLOBS model and the Kalman model with or without the decay term inclusion; however, these three models accounted for a significantly greater amount of variance in the data than the other five models. The results from the ROI main effect are shown in Figures 7.39 and 7.40.

There was also a significant interaction effect between METHOD and ROI. This was investigated to determine if the exponential model was driving the effect. Based on the results of Specific Aim 4, an interaction between the olfactory ROI and the Kalman filter decay model was expected. The interactions are shown in Figures 7.41, 7.42, 7.43 and 7.44.

These interaction results showed that the exponential term inclusion detracted from the Kalman filter model in accounting for variability in the olfactory ROI. However, the
Figure 7.38 Significant main effect of METHOD trained on the left hemisphere to predict the right in session one, including the decay model.

Figure 7.39 Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one, including the decay model.

Figure 7.40 Main Effect of ROI trained in the left hemisphere and tested on the right for data from session one, including the decay model.

Exponential term improved the Kalman filter model in the amygdala, insula, hippocampus and posterior cingulate.
Figure 7.41  Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.

Figure 7.42  Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.

Figure 7.43  Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.

Figure 7.44  Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session one, including the decay model.
Using the Right Hemisphere to Predict the Left  The ANOVA results for olfactory data, session one, training on the data from the right hemisphere and testing on data from the left, are shown in Table 7.12.

Table 7.12  ANOVA Results for Olfaction Data, Session One, Right Hemisphere Predicting Left, Including Decay

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>7546.8</td>
<td>19</td>
<td>397.2</td>
<td>2.82</td>
<td>0.0002</td>
</tr>
<tr>
<td>Method</td>
<td>14494.9</td>
<td>7</td>
<td>2070.7</td>
<td>8.6</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>3415.4</td>
<td>133</td>
<td>25.68</td>
<td>1.87</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>16422.6</td>
<td>1197</td>
<td>13.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>127132</td>
<td>1599</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These results show a main effect of METHOD, see Figure 7.45. When investigated with Scheffé post-hoc tests, these results showed there was no significant difference between the FLOBS model and the Kalman model with or without the decay term inclusion; however, these three models account for a significantly greater amount of variance in the data than the other five models. The results from the ROI main effect are shown in Figures 7.46 and 7.47.

There was also a significant interaction effect between METHOD and ROI. This was investigated to determine if the exponential model was driving the effect. Based on the results of Specific Aim 4, an interaction between the olfactory ROI and the Kalman filter decay model was expected. The interactions are shown in Figures 7.48, 7.49, 7.50 and 7.51.

These interaction results showed that the exponential term inclusion detracted from the Kalman filter model in accounting for variability in the olfactory ROI. However, the exponential term improved the Kalman filter model in the amygdala, piriform, thalamus, and anterior and posterior cingulate.
Figure 7.45  Significant main effect of METHOD trained on the right hemisphere to predict the left in session one, including the decay model.

Figure 7.46  Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one, including the decay model.

Figure 7.47  Main Effect of ROI trained in the right hemisphere and tested on the left for data from session one, including the decay model.
Figure 7.48 Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

Figure 7.49 Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

Figure 7.50 Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

Figure 7.51 Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.
**Figure 7.48** Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

**Figure 7.49** Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

**Figure 7.50** Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.

**Figure 7.51** Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session one, including the decay model.
7.6 Dependence of the Kalman Filter on its Training Data

To show that the results from the application of the Kalman filter are not imposing some bias into the results within subject, within ROI and across stimuli comparisons are made. This analysis only varied the stimulus and tested within subjects and ROI. The within ROI and subject constraints ensured the noise structure was the same across comparisons.

Two ROI were chosen, Brodmann Area 17, a typical visual stimulus ROI and the piriform cortex, a typical olfaction ROI. Constricting data to within the ROI, the Kalman filter was trained on either visual stimulus data or olfactory data. The extracted response from the training data was used to create a test design for the test data. A second run of data, with the same stimulus, was then tested within the ROI using the training information. The percentage of variance explained by this model was then used as an independent variable in an analysis of variance.

There were then three factors in this analysis each having two levels. The factors were hemisphere, with left and right levels, training data, with visual and olfactory levels, and test data, with visual and olfactory data levels.

7.6.1 Visual Data

Restricting analysis to the visual ROI (BA 17) first, the ANOVA table is shown in Table 7.13. This shows there were significant main effects of Training Data and Test Data. There was also an interaction between the two factors. These results were investigated with Scheffé post-hoc tests to reveal that the effects of the visual training and test data were significantly greater than the effects of the olfactory training and test data, as expected and shown in Figures 7.52 and 7.53. The interaction term was driven by the effect of visual training data interacting with the visual test data, and shown in Figure 7.54. Scheffé post-hoc tests with an alpha equal to 0.05 showed that olfactory training + olfactory testing < olfactory training + visual testing t(27)=−6.0231, p=1.9906e-006, olfactory training + olfactory testing < visual training + visual testing t(27)=−15.2256, p=8.9616e-015, visual training + olfactory testing < olfactory training + visual testing t(27)=−5.8447, p=3.1888e-006, visual training
Table 7.13 ANOVA Table Within Visual ROI (BA 17)

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training Hemisphere</td>
<td>93.3</td>
<td>1</td>
<td>93.3</td>
<td>4.92</td>
<td>0.0684</td>
</tr>
<tr>
<td>Test Hemisphere</td>
<td>2.3</td>
<td>1</td>
<td>2.3</td>
<td>0.02</td>
<td>0.891</td>
</tr>
<tr>
<td>Train Data</td>
<td>5792.1</td>
<td>1</td>
<td>5792.1</td>
<td>23.63</td>
<td>0.0028</td>
</tr>
<tr>
<td>Test Data</td>
<td>19427.8</td>
<td>1</td>
<td>19427.8</td>
<td>69</td>
<td>0.0002</td>
</tr>
<tr>
<td>Train Hemi*Test Hemi</td>
<td>7.8</td>
<td>1</td>
<td>7.8</td>
<td>0.18</td>
<td>0.6717</td>
</tr>
<tr>
<td>Train Hemi*Train Data</td>
<td>51.3</td>
<td>1</td>
<td>51.3</td>
<td>1.19</td>
<td>0.2799</td>
</tr>
<tr>
<td>Train Hemi*Test Data</td>
<td>41.9</td>
<td>1</td>
<td>41.9</td>
<td>0.97</td>
<td>0.3282</td>
</tr>
<tr>
<td>Test Hemi*Train Data</td>
<td>24.9</td>
<td>1</td>
<td>24.9</td>
<td>0.58</td>
<td>0.4502</td>
</tr>
<tr>
<td>Test Hemi*Test Data</td>
<td>72.5</td>
<td>1</td>
<td>72.5</td>
<td>1.67</td>
<td>0.1998</td>
</tr>
<tr>
<td>Train Data*Test Data</td>
<td>5820.9</td>
<td>1</td>
<td>5820.9</td>
<td>134.53</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>3072</td>
<td>71</td>
<td>43.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39999.7</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ olfactory testing < visual training + visual testing $t(27)=-14.96$, $p=1.3728e-014$, olfactory training + visual testing < visual training + visual testing $t(27)=-8.7174$, $p=2.4749e-009$.

Figure 7.52 Mean and standard errors within the Visual ROI (BA 17) collapsed across test data for olfactory and visual training data.

Figure 7.53 Mean and standard errors within the Visual ROI (BA 17) collapsed across training data for olfactory and visual test data.

An example, taken from a single subject, of what this analysis really involved is shown in Figure 7.55. This figure shows the design created from the Kalman filter extracted results for the two ROIs for the both hemispheres. These responses were extracted from the first session of visual data. This shows that within the visual ROI the extracted response was
Figure 7.54 Mean and standard errors within the Visual ROI (BA 17) for training/test combinations.

very robust and clearly showed task related signal change. It is of interest to note that there also appeared to be task related signal change in the olfactory ROI. These designs were used as models for testing the second session of visual data to determine which accounted for the greatest percentage of variance in the data.

Figure 7.55 Example designs created from training on the first data set to be tested against the second data set within the visual ROI (BA 17).
7.6.2 Olfactory Data

Restricting analysis to the olfactory ROI (piriform cortex) the ANOVA table is shown in Table 7.14. This shows there was a significant main effect of Training Hemisphere. There was also an interaction between the Training Data and Test Data. These results were investigated with Scheffé post-hoc tests to reveal that the effect of the Left Training Hemisphere was greater than the effect of the right Training Hemisphere, and shown in Figure 7.56. The interaction term was driven by the effect of olfactory training data interacting with the olfactory test data, and shown in Figure 7.57. Scheffé post-hoc tests with an alpha equal to 0.05 showed that olfactory training + olfactory testing > visual training + olfactory testing \( t(27)=4.5353, p=0.00010615 \), olfactory training + olfactory testing > olfactory training visual testing \( t(27)=3.8636, p=0.00063415 \), olfactory training + olfactory testing > visual training + visual testing \( t(27)=3.3934, p=0.0021463 \).

Table 7.14 ANOVA Table Within Olfactory ROI (Piriform Cortex)

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Training Hemisphere</td>
<td>186.74</td>
<td>1</td>
<td>186.736</td>
<td>0.0486</td>
</tr>
<tr>
<td>Test Hemisphere</td>
<td>43.28</td>
<td>1</td>
<td>43.283</td>
<td>0.2273</td>
</tr>
<tr>
<td>Train Data</td>
<td>504.82</td>
<td>1</td>
<td>504.818</td>
<td>0.0643</td>
</tr>
<tr>
<td>Test Data</td>
<td>543.83</td>
<td>1</td>
<td>543.864</td>
<td>0.1666</td>
</tr>
<tr>
<td>Train Hemi*Test Hemi</td>
<td>0.75</td>
<td>1</td>
<td>0.748</td>
<td>0.8483</td>
</tr>
<tr>
<td>Train Hemi*Train Data</td>
<td>6.8</td>
<td>1</td>
<td>6.802</td>
<td>0.5644</td>
</tr>
<tr>
<td>Train Hemi*Test Data</td>
<td>3.49</td>
<td>1</td>
<td>3.492</td>
<td>0.6794</td>
</tr>
<tr>
<td>Test Hemi*Train Data</td>
<td>34.46</td>
<td>1</td>
<td>34.464</td>
<td>0.1966</td>
</tr>
<tr>
<td>Test Hemi*Test Data</td>
<td>54.59</td>
<td>1</td>
<td>54.591</td>
<td>0.1053</td>
</tr>
<tr>
<td>Train Data*Test Data</td>
<td>553.33</td>
<td>1</td>
<td>553.333</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>1440.17</td>
<td>71</td>
<td>20.284</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6171.44</td>
<td>111</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7.56 Mean and standard errors within the olfactory ROI for the main effect of Training Hemisphere.
An example, taken from a single subject, of what this analysis really involved is shown in Figure 7.58. This figure shows the design created from the Kalman filter extracted results for the two ROIs for the both hemispheres. These responses were extracted from the first session of olfactory data. This shows that within the olfactory ROI the extracted response was very robust and clearly shows task related signal change, in particular in the right hemisphere. These designs were used as models for testing the second session of olfactory data to determine which accounted for the greatest percentage of variance in the data.

**Figure 7.57** Mean and standard errors within the Olfactory ROI for training/test combinations.

**Figure 7.58** Example designs created from training on the first data set to be tested against the second data set within the olfactory ROI (piriform cortex).
7.7 Prediction Error across Time

Implicit in the derivation of the Kalman filter is a decreasing amount of estimation noise as data is incorporated into the filter. This is shown to be true through the following figures. The data from all subjects for the olfactory data was averaged over the first scanning session. The Kalman filter was then applied and the extracted response along with the estimation error is plotted in Figures 7.59 and 7.60. The plots show the extracted response at various experimental time points for the right piriform ROI and the left olfactory ROI.

![Figure 7.59](image1.png)

**Figure 7.59** Estimate of extracted response at four time points from the right piriform ROI for the group mean and standard errors. The time points are: A 60, B 120, C 180 and D 240 seconds from the start of the experiment.

![Figure 7.60](image2.png)

**Figure 7.60** Estimate of extracted response at four time points from the left olfactory ROI for the group mean and standard errors. The time points are: A 60, B 120, C 180 and D 240 seconds from the start of the experiment.
CHAPTER 8
DISCUSSION

8.1 Visual Data

Results from the visual experiment are promising as they showed task related signal change in expected regions [65]. This gives evidence that the stimuli chosen were appropriate. The reason for including this experimental manipulation was as a test for the proposed method. Verification of Kalman filter’s application to fMRI data was needed before application to data with a stimulus that has shown differential responses, such as odorants [66][67].

This verification was performed with two flashing checkerboard visual stimuli experiments. The first experiment presented the stimulus for 2 seconds, and the second for 12 seconds. The motivation was, if the olfactory system displayed differential time courses across brain regions [3], than the resultant task related signal changes from the visual experiments would mimic this behavior. To accurately mimic the expected olfactory behavior, the timing between the sustained visual stimulus and the odorant stimuli were identical (12 seconds “on” and 30 seconds “off”). The transient stimulus was designed to mimic the transitory behavioral observed in the olfactory system [2][3] by only presenting the stimulus for 2 seconds alternated with a 40 second “off” period.

The visual experimental data was analyzed with the Kalman filter to extract the underlying response to the stimuli in all ROIs. Upon inspection of these responses, the sustained stimulus responses had a wider response than the transient stimulus. T-tests showed this to be true in bilateral BA17 and BA18 and in right Calcarine fissure. The fact that the extracted responses differed in their widths showed the applicability of the Kalman filter to the analysis of fMRI data.

It is worth noting the lack of extracted responses in the olfactory regions during the visual stimulation. A benefit of an analysis tool, is to give expected results in expected
regions, one should also consider regions where no result is expected. For example in the olfactory ROI the extracted responses are all relatively flat.

8.2 Olfaction Data

The results obtained from the olfactory group data are promising, given the previous unreliability of fMRI and olfaction [1]. Task related signal change was evident in all ROI, even those only expected to show involvement in the visual experiment, BA17, BA18, calcarine fissure and fusiform. The most significant signal changes occurred in the amygdala (96.96 /81.10 R /L percentage of ROI reaching significance), entorhinal (58.65% /38.67% R/L), inferior frontal orbit (2.929% /32.98% R/L), hippocampus (24.75% /28.64% R/L), insula (55.70% /47.74% R/L), middle cingulate (33.77% /33.87% R/L), and piriform (88.01% /90.46% R/L).

The robustness of the response could be from a number of reasons. A larger set of odors (ten) was used than in previous experiments which showed odorant habituation over experimental time [2][3]. This larger set of odors, which did not repeat within a session, was used to maintain elevated responses to odorants by each being relatively novel. Odorants were also presented for twelve seconds each. This length of stimulus was longer than the typical 500 to 2000ms length used in event-related designs [68]. Furthermore, in other modalities stimulus presentations have shown an additive response to fMRI signal amplitude change [17] where block designs show stronger responses. The odorant stimulus was also of a length which should decrease the amount of within trial habituation as shown in previous olfactory experiments [4][3]. This careful experimental planning combined with four experimental repetitions, has produced an experimental manipulation with robust task related signal change.

The general linear model analysis of this data also employed flexible basis functions [40]. These basis functions were created using a collection of half cosine functions, which are shown in Figure 8.1. The half cosine functions describe the four segments of the
hemodynamic response function, the initial delay which could include an initial dip, a ramped increase, a ramped decrease to potentially post-stimulus levels and the return to baseline levels. In the work by Woolrich et al. 2004, the authors found three basis functions that most effectively span the subspace of all possible hemodynamic responses, these are shown in Figure 8.2. These three basis functions were convolved with an *a priori* habituating model of activity in response to odorant stimuli as discussed in [3]. The model consisted of an exponential decaying function at the start of every odorant presentation.

From this data, averages were computed in every ROI, in both hemispheres, in all four sessions of data and across subjects. The result is forty average time series per session per subject. Data from the first session was used to train the filter to the data. This process estimated the underlying variance components of the data. The second session of data was then tested with these values to extract the underlying responses. From these estimates,
Figure 8.2 Half-cosine basis set.

The width of the responses were calculated. The hypothesis from this analysis was that the responses would differ between the primary and the secondary olfactory regions.

The primary olfactory ROIs were expected to show rapidly habituating responses, similar to the extracted response to the transient visual stimulus. The secondary olfactory ROIs were expected to display sustained responses to the odorants similar to the response to the sustained visual stimulus. Comparing the width of the responses across primary and secondary olfactory regions showed no significant differences. This was in opposition to the hypothesis of these regions showing differential time courses.

The orbital frontal regions were expected to show responses that maintained a high level of task related signal change [3]. This region showed significant involvement in the processing of the presented odorants in approximately 30 percent of the inferior frontal orbit region of interest. However, when the underlying response was extracted, it showed a response with a width of 11.8 seconds in the right hemisphere and 7.1 seconds in the left. At first this supports the hypothesis; however, the standard error of these values are 8.4
and 4.1 respectively. The result was no significant difference from the primary olfactory regions.

One reason for this, was the difficulty in scanning the orbitofrontal regions of the brain. These regions typically show significant signal dropout caused by tissue interfaces [69]. This signal loss is greatest when there are large magnetic susceptibility differences, for example at bone and air interfaces such as in the sinuses. Different groups have addressed this problem in different ways.

The work by Deichmann et al. 2003 developed a z-shimming approach to recover signal in the orbitofrontal regions [52]. To do this, the authors first used a slice angle of thirty degrees. This was instead of scanning the brain parallel to the AC-PC line in the axial orientation. This had been shown to decrease the amount of signal dropout [69]. The authors performed tests to find that thirty was indeed an optimal angle. In addition, the thirty degree tilt orients drop-out gradient to be perpendicular to the slice selection magnetic gradients. Therefore, the authors were able to use a preparation gradient (the z-shim) perpendicular to the slice selection angle to cancel out the drop-out gradient. This technique was shown to improve signal in the orbitofrontal regions; however, with a cost of sacrificing sensitivity in other regions. In regions where there was no drop out gradient, the z-shimming caused an increase in signal drop-out [52].

As the study conducted in this work was interested in multiple brain regions, primary and secondary olfactory cortices and visual, a compromise was taken in regards to this technique. All scans were done at the angle of thirty degrees to the AC-PC line; however, no z-shim pulse was applied.

The z-shim technique was used in the olfactory work by Gottfried [68][5] [70][71]. The olfactory work by Sobel et al. used different techniques to address the signal loss issue. In their 1997 work, local surface coils were used [72]. These were oriented to maximize the orbitofrontal signal. In other work from the same lab, spiral image acquisition at an angle of thirty degrees was used. This was the same as previously used [52]; however, the
spiral image acquisition employed was still affected by the signal drop out [73]. In their other work, this lab focused on the olfactory effects in the cerebellum thereby avoiding the issue [66].

One promising technique to recover signal loss is the use of localized shimming techniques [73]. These techniques use second order shims to reduce drop out. This is in contrast to the other global z-shim technique [52]. The higher order order local shims allow gradients to be applied to one particular brain region without affecting the entire brain. This technique would therefore eliminate the drawback of global shimming. This is very promising and has shown task related signal change in the orbitofrontal brain regions in response to odorant presentation. Unfortunately, it was not possible to implement on the scanner used. Therefore, it was possible to employ the Deichmann et al. 2003 [52] technique but not that of Wilson et al. 2002 [73]. The planned installation of a 3.0 Tesla Philips scanner will be equipped with local shim abilities thereby allowing the implementation of this technique.

Returning to the data and investigating how much of each ROI was actually scanned consistently across subjects revealed the extent of drop out. Table 8.1 shows the ROI and the number of voxels in the ROI scanned, the total size of the ROI and the percentage scanned.

The two most affected ROIs (middle and superior orbital frontal) and the actual voxels included from all subject overlaid on a background anatomical image are shown in Figure 8.3. This shows that a large portion of the region of interest expected to show sustained signal change in response to odorant stimulation was lost. The portions of these ROIs that remained were averaged over. The result may have been an average over voxels that were distorted by the signal dropout of their neighbors [69][73]. The analyses by Sobel et al. 2000 [3] that show sustained task related signal change in the frontal orbit regions, were based on data from nine voxels chosen based on their anatomical location. This suggests that a careful search of the frontal orbit ROIs could lead to similar results.
Table 8.1 Percentage and Actual Size of ROIs Scanned in All Subjects

<table>
<thead>
<tr>
<th>ROI</th>
<th>% ROI &gt; scanned (R/L)</th>
<th>Voxels Scanned (R/L)</th>
<th>Voxels Total (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA 17</td>
<td>83.89/92.65</td>
<td>557/630</td>
<td>664/680</td>
</tr>
<tr>
<td>BA 18</td>
<td>89.08/86.10</td>
<td>2921/2849</td>
<td>3279/3309</td>
</tr>
<tr>
<td>amygdala</td>
<td>100/100</td>
<td>461/508</td>
<td>461/508</td>
</tr>
<tr>
<td>anterior cingulate</td>
<td>99.09/99.95</td>
<td>2400/2196</td>
<td>2422/2197</td>
</tr>
<tr>
<td>calcarine</td>
<td>92.46/98.26</td>
<td>3127/2652</td>
<td>3382/2699</td>
</tr>
<tr>
<td>entorhinal</td>
<td>98.46/100</td>
<td>319/331</td>
<td>324/331</td>
</tr>
<tr>
<td>frontal inf. orbital</td>
<td>88.88/87.72</td>
<td>2238/2250</td>
<td>2518/2565</td>
</tr>
<tr>
<td>frontal mid. orbital</td>
<td>40.49/24.52</td>
<td>590/400</td>
<td>1457/1631</td>
</tr>
<tr>
<td>frontal sup. orbital</td>
<td>27.52/26.14</td>
<td>485/482</td>
<td>1762/1844</td>
</tr>
<tr>
<td>fusiform</td>
<td>96.47/94.59</td>
<td>3639/3845</td>
<td>3772/4065</td>
</tr>
<tr>
<td>hippocampus</td>
<td>100/100</td>
<td>1697/1728</td>
<td>1697/1728</td>
</tr>
<tr>
<td>insula</td>
<td>100/100</td>
<td>3329/3180</td>
<td>3329/3180</td>
</tr>
<tr>
<td>mid. cingulate</td>
<td>100/100</td>
<td>2923/3301</td>
<td>2923/3301</td>
</tr>
<tr>
<td>olfactory</td>
<td>94.01/93.77</td>
<td>581/602</td>
<td>618/642</td>
</tr>
<tr>
<td>orbital frontal/BA 47</td>
<td>91.32/90.07</td>
<td>1473/1443</td>
<td>1613/1602</td>
</tr>
<tr>
<td>parahippocampal</td>
<td>99.45/99.65</td>
<td>1802/2014</td>
<td>1812/2021</td>
</tr>
<tr>
<td>piriform</td>
<td>100/100</td>
<td>267/262</td>
<td>267/262</td>
</tr>
<tr>
<td>post. cingulate</td>
<td>100/100</td>
<td>898/717</td>
<td>898/717</td>
</tr>
<tr>
<td>sup. temporal pole</td>
<td>93.34/94.48</td>
<td>2033/2122</td>
<td>2178/2246</td>
</tr>
<tr>
<td>thalamus</td>
<td>100/100</td>
<td>1646/1605</td>
<td>1646/1605</td>
</tr>
</tbody>
</table>

Figure 8.3 Overlay of the two ROIs most affected by signal drop out and all voxels included in this analysis. All are overlaid on the mean of all ten subjects’ anatomical images.
8.3 Comparison of Statistical Models

8.3.1 Visual Data

In an attempt to increase the sensitivity of the statistical models, Cerf-Ducastel and Murphy 2004 [64] compared a stimulus based model and a perception based model. The stimulation model was the exact timing parameters of the odorant presentations. The perception model was created from the subject's rating of the perceived intensity over time during post-scanning re-administration of the odorants. This was intended to be a better predictor of task related signal change. Their results showed the perception based model was better than the stimulation model at elucidating responses to odorants.

The authors compared their models in an analysis of variance (ANOVA) framework. This approach was taken in this work to compare a variety of models. Recall that the models included in this analysis were: the experimental stimulus timing (12 seconds on, 30 seconds off), a six second delayed version of the experimental stimulus, the experimental timing convolved with a single gamma function, the experimental timing convolved with the double gamma model, a model with a shortened on time convolved with the double gamma model (6 seconds on and 36 seconds off), a model derived from the estimate of the underlying signal as derived from the previous run of data, and a model with a rapidly decaying exponential function convolved with three optimal basis functions.

Expected results from this analysis on the visual data were that the stimulus timing convolved with the difference of two gamma functions model and the Kalman filter derived model would dominate. Results showed a main effect of region and of statistical model. The main effect of ROI was driven by BA17, BA18 and the Calcarine fissure as evaluated by Scheffé post-hoc tests. Post-hoc tests showed that the main effect of model was driven by the Gamma model, the Standard model, the basis set model and the Kalman model. These models were significantly better at predicting variance in the data than the other three. These results showed that the modeled undershoot of the Standard model did not increase statistical sensitivity over the Gamma model, which did not account for the undershoot.
These results also show that the Basis set model accounts for similar levels of variance in the data as the Standard model. The expected result was also achieved, that the Kalman filter model would account for similar levels of variance in the data as the Standard model. These results show that for data sets where the subjects are engaged in a visual stimulus, one session of data may be used for the creation of a statistical model for a subsequent data session. The results support those previously presented in the literature [37].

8.3.2 Olfaction Data

Expected results from the analysis on the olfaction data were that the dominant models would be the Kalman filter model, the basis set model and the model with the shortened “on” time. The Kalman filter model was based on *a priori* data and therefore would be well informed at predicting the subsequent experimental session. The two other models were expected to also have superior performance, because they were based on previous literature about the nature of the task related signal changes to odorant stimuli [4][3].

Results for the ANOVA showed a main effect of ROI but no significant effect of METHOD. Post-hoc tests showed that the main effect of ROI was driven by the piriform, amygdala and the insula. Even though the effect of model was non-significant it was investigated to show that the three models that accounted for the greatest variance were the Kalman filter, the basis set and the Poellinger models.

This non-significant result may be the fault of the Kalman filter method, or may expose underlying effects occurring in the brain. The data sets used in this analysis were the result of identical stimuli; however, the data was not collected consecutively in time. The visual data sets were interspersed with the olfactory scans. This interspersion allowed extra time, approximately 5 minutes, between olfactory sessions to limit habituation. The lack of prediction may be the result of this task modality change. The effect of task switching may result in one session’s worth of data not predicting future data sets, even when the stimuli were identical. Another hypothesis may be, that it is not reasonable to assume one data set
will predict others. This is not addressable with the data from this experiment, but it is of interest for future work.

8.3.3 Cross Hemisphere Prediction

Recall that the overall hypothesis of this project was to extract time varying changes from fMRI data sets. If the physiologic effect of a varying signal were occurring, than prediction of future time points was confounded with the time varying effects. To circumvent this, data from one hemisphere was used as a predictor of the opposite hemisphere within a region of interest.

The model comparison analyses were redone; however, the training data set for the basis set model and the Kalman filter model was the opposite hemisphere of interest. The result was that any time varying effects were common and not confounding. The assumption was made that time varying effects were similar across hemispheres.

As the results were similar using the left hemisphere to predict the right and using the right to predict the left, the common results are discussed. The results for the olfactory data from session one showed significant main effects of method and ROI. This was in contrast to the non-significant main effect of method when one session was used to predict the next session. This main effect of method was driven by the basis set model and the Kalman filter derived model. The two models were not significantly different from each other. The result was that the Kalman filter model was no better than the a priori specified basis set model.

Interestingly, when the subsequent sessions of olfactory data were investigated, the situation changed. For both hemispheres of session two, the right hemisphere of session three and both hemispheres of session four, the Kalman filter model accounted for significantly greater amounts for variance in the data than all other models. This result was highly encouraging because it showed that without any a priori information, the Kalman filter model was able to describe opposite hemisphere task related signal change, better than the other models.
8.3.4 Tracking Time Dependent Changes

One feature not addressed up to this point, is the fact that the Kalman filter is able to track a signal across time, and not just deconvolve an underlying response. The previous results could have been similarly obtained with deconvolution techniques such as described by Glover 1999 and Goutte et al. 2000 [17][39].

Every step was taken in the design of this experiment to limit the amount of habituation in response to repeated odorant stimulation. However, temporally decaying behaviors were still extracted. This was done by investigating the peak response to odorants at every experimental time point.

The Kalman filter's main difference from statistical analyses that process data in a batch, like linear regression or deconvolution, is its ability to extract the response from every time point. From each of these estimates, the peak amplitude was taken. This was typically six seconds after the start of odorant presentation. From these values a simple model was fit to them, a single exponential. Although more complicated models may have been chosen, the simplest was employed for parsimony and precedence. In the work by Sobel et al. 2000 [3] the authors modeled two exponential decays in their olfactory data, one over stimulus presentation and one over experimental time. Likewise Gottfried et al. [5] also model an exponential decay over time. These authors specified the rate of decay *a priori* and therefore did not let the data show the amount of cross experimental habituation.

Once the exponential model was fit to the peak response, this decay rate term was used in an ANOVA model. The results showed a main effect of ROI. Post-hoc tests revealed that the olfactory ROI drove this effect. It was not surprising to find no significant decay effect in the piriform cortex because of the changing odors.

8.3.5 Exponential Information and the Kalman Filter Model

Once determined that time varying behavior existed in the data, this information was used to determine if it would increase the Kalman filter's predictions of the opposite hemisphere.
To do this, the model comparison analyses were redone with the inclusion of an eighth model. This was the Kalman filter model multiplied by the exponential term as calculated in Section 7.5. The expected results from this analysis were again, a main effect of model driven by the Kalman filter and exponential term. Also hypothesized, was a significant interaction between the Kalman filter and exponential term model and the olfactory ROI. This was based on the fact that this ROI showed an exponential decay significantly different from all other ROIs.

The results did indeed show a main effect of model; however, there was no significant difference between the three models driving this effect, the basis set model and the two Kalman filter models. Surprisingly, investigation of the significant interaction between model and ROI was not driven by the olfactory ROI interacting with the exponential Kalman model. In this ROI the amount of variance accounted for actually decreased upon inclusion of the exponential term. The greatest interaction occurred in the amygdala, piriform, thalamus and cingulate ROIs.

It is worthwhile to comment on the Kalman filter model creation. The Kalman filter based model was created through the concatenation of estimated responses to stimuli. Therefore, after the complete analysis of one session of the data, the Kalman filter estimate was the response to the stimuli train. This response was concatenated five times to produce the Kalman filter based model. This analysis assumed that the response to each odorant within a session was the same. The time tracking advantages of the Kalman filter were only exploited through the use of fitting the exponential model to the extracted responses. This tested for amplitude habituation across the sessions. The implementation of the Kalman filter in this work showed that the method was better at creating static estimates of the underlying signal than tracking it through time. Future work will take further advantage of the tracking abilities of the adaptive filter by using the estimate of the response over time.
8.4 Training Data Dependence

The Kalman filter was tested to ensure that it was not imposing bias on the data it was analyzing. This was tested by choosing two ROIs, one related to the visual experiment (the BA17 ROI) and one related to the olfaction experiment (the olfactory ROI). The Kalman filter was trained in both of these ROIs with data from the first session of the visual experiment and the first session from olfaction. Data from the second session of the visual experiment and from the second session of olfaction in the two ROIs were then used as test data. This analysis was done to show that when trained on data from the same experimental manipulation, the Kalman filter derived design, accounted for more variance in subsequent test data than when trained on different experimental data.

Results from an ANOVA showed that there was indeed an interaction between training data and test data. This effect was driven by visual training data combined with visual test data in the BA17 ROI. Likewise, in the olfactory ROI the same main effect was found and driven by the interaction of olfactory training data and olfactory test data.

8.5 Prediction Error across Time

The function of the Kalman filter was to predict the response in the next data point and then refine that prediction as the next data point became available. Therefore, the prediction error should decrease over experimental time. A decrease in prediction error also increases the confidence in the estimated response. By reexamining the equation that calculates the prediction error this was shown. This equation is reproduced below:

\[
K(n + 1, n) = F(n + 1, n)K(n, n - 1)F^T(n + 1, n) - G(n)R^T(n)G^T(n) + Q_1(n)
\]

First, recall that the \(F\) term was the transition matrix and was set to be identity. Therefore, the next prediction error, was the previous prediction error plus an adjustment. The second right hand term was negative and the third was positive; therefore as long as the second term exceeds the variance of the state noise, the prediction error will decrease. This was
shown with experimental data that was averaged over all subjects. In the beginning of the experiment the prediction error was quite high but quickly reduced.

### 8.6 Paced Breathing

This experiment used paced breathing for all olfactory stimulation. This was in contrast to the work by others who had subjects sniffing in their experiments [74][66][3]. The use of sniffing ensured that the subjects were sampling the odor space they were presented with. The proper pacing of breath also ensured this. The rate of breathing was chosen so that the subjects were comfortable during the experiment. This rate was restricted between 10 and 12 breaths per minute. Once a rate was decided, it and the phase of the breathing cycle to start at, were adjusted. The reason for these adjustments was to ensure that all subjects maximally sampled the odorants.

Maximal sampling involved having the subjects inspire at the onset of every odorant. This could have been ensured in two ways. One was a phase shift between each odorant presentation, and the other was an initial adjustment of the breathing rate. For example, if the breathing rate was decided at 12 breaths per minute, this corresponded to 0.2 breaths per second. The experimental timing was such that one odorant was presented every 42 seconds. Therefore, the subject must inspire every 42 seconds. The number of breaths taken in 42 seconds at a rate of 0.2 breaths per second was 8.4. This was rounded to 8 breaths per 42 seconds, which corresponded to 11.4 breaths per minute. This was then set as the subject’s paced breathing rate.

Since the initial “off” period of the experiment was not 42 seconds but rather 30 seconds, the phase of the breathing cycle was also calculated. This was done by determining at what point in the cycle the subject must start breathing so they inspired at the first odorant presentation. These calculations were performed by the odorant presentation program once the experimenter entered the set breathing rate of 10, 11 or 12. The result
was that every odorant was sampled by the subject as soon as it was presented and the
subject only had to adjust their breathing at the start of the experiment.

The use of paced breathing instead of sniffing also eliminated sniffing related activity. It has been shown that sniffing induced task related signal change in the piriform cortex even when no odorant was present [74]. Using a non-sniffing paradigm ensured that task related signal change in the piriform was not the effect of sniffing but the result of the presented odorants.

8.7 Stimulus Presentation Programs
The conduction of an olfaction experiment involved quite a bit more hardware than experiments such as a flashing checkerboard visual experiment. There was the integration of the olfactometer control, the respiration data collection, the behavioral response collection and the breathing pacer. The control of these factors was done using a single LabView program executed on a single laptop. To facilitate the monitoring of the experiment as it was conducted, the programs were written so they presented information on two separate monitors. This resulted in a simple screen that that was presented to the subject and a feedback and control screen for the experimenter.

While the experiment took place, the experimenter could see the breathing trace and a trace of the breathing pacer to make sure the subjects were following it. The experimenter could also observe the reactions of the subject to the odorants via the button box. Every button press the subject made was shown on the screen. The experimenter could also see at what point the experiment was, for example how many odors had been presented and how many were left.
CHAPTER 9
CONCLUSION

This work was the second attempt at tracking a time varying signal in fMRI data [11]. This was however, the first attempt at extracting the response to a stimulus and tracking it over time. Testing the method on the visual data provided conclusive evidence that the Kalman filter method is applicable to fMRI data. The subsequent tests on the olfaction data however, did not provide hypothesized results. One explanation for this was that the experimental design was not appropriate for extracting differential responses to odorants across the primary and secondary cortices. Follow-up experiments could include much longer odorant stimulations, on the order of sixty seconds, to exaggerate this effect [4].

It was hypothesized that inclusion of subject, regional, and task specific information into analyzing olfactory data would increase the sensitivity of statistical tests over that of a prior models. The Kalman filter model did not perform significantly different from other models when using one session of data to predict the subsequent data set. The reason for this was because of the confounding effect of time varying changes in the data. These effects were controlled for using cross hemisphere predictions. For all sessions of data except the first, the Kalman filter accounted for significantly greater variance in the data than all other models.

The most significantly useful employment of the Kalman filter was in its extraction of time varying changes in the data. This ability to effectively track changes in the data, showed the applicability of the method at providing unobtainable information from methods such as linear regression. The inclusion of this time varying behavior into the model comparison analyses did not improve the sensitivity of the Kalman filter model.

Overall, the results of this work showed the effectiveness the Kalman filter at extracting the shape of the hemodynamic response to visual and olfactory stimuli. This work also showed the flexibility of the basis function set at detecting task related signal change
from differently shaped responses. Future work could use a basis function set approach to statistical parametric mapping to locate functional regions of interest (fROI), instead of the anatomical ROIs used here. These fROI could then be analyzed using the Kalman filter to detect and track time varying changes in the data. This combination of fMRI data analysis with the basis set and the Kalman filter would provide an effective approach to the analysis and understanding of fMRI data.
APPENDIX A
LINEAR ALGEBRA

Review of some Matrix algebra properties. $A$, $B$ and $C$ all represent square matrices, $I$ is the identity matrix and $s$ is a scaler quantity. These properties were referred to in Chapter 4.

1. $(AB)C = A(BC)$

2. $A(B + C) = AB + AC$

3. $(A + B)C = AC + BC$

4. $AB \neq BA$

5. $(AB)^{-1} = B^{-1}A^{-1}$

6. $AA^{-1} = A^{-1}A = I$

7. $(AB)^T = B^T A^T$

8. $(A^{-1})^T = (A^T)^{-1}$

9. $(A + B)^T = A^T + B^T$

10. $sA = A^T s$
APPENDIX B

EXTRA RESULTS

B.1 Olfaction Data from Session Two

B.1.1 Left to Predict Right Hemisphere in Session Two

The ANOVA results for olfactory data, session two, training on the data from the left hemisphere and testing on data from the right, are shown in Table B.1.

Table B.1 ANOVA for Olfaction Data, Session Two, Left Hemisphere Predicting Right

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>1585.1</td>
<td>19</td>
<td>83.43</td>
<td>1.95</td>
<td>0.0136</td>
</tr>
<tr>
<td>Method</td>
<td>3161.8</td>
<td>6</td>
<td>526.974</td>
<td>13.72</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>1768.8</td>
<td>114</td>
<td>15.516</td>
<td>1.92</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>8278.4</td>
<td>1026</td>
<td>8.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29557.3</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.1 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method accounts for a significantly greater percentage of the variance in the data than all other methods.

The main effect of ROI is shown in Figures B.2 and B.3 and these results were investigated using Scheffé post-hoc tests. The Scheffé post-hoc tests show the left hemisphere regions that predict their contra-lateral hemispheres significantly better than other regions at a threshold of alpha equal to 0.05. The amygdala is significantly different from BA17, BA18, AC, calc, entorhinal, f inf orb, f mid or,b fus, hipp, olf, f orb/BA47, parahipp, post cing, temp pole and thal. The insula is significantly different from entorhinal, parahipp and temp pole. The piriform is significantly different from temp pole.
Figure B.1  Significant main effect of METHOD trained on the left hemisphere to predict the right in session two.

Figure B.2  Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two.

Figure B.3  Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two.
B.1.2 Right to Predict Left Hemisphere in Session Two

The ANOVA results for olfactory data, session two, training on the data from the right hemisphere and testing on data from the left, are shown in Table B.2.

Table B.2 ANOVA for Olfaction Data, Session Two, Right Hemisphere Predicting Left

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>2487.36</td>
<td>19</td>
<td>130.914</td>
<td>2.47</td>
<td>0.0011</td>
</tr>
<tr>
<td>Method</td>
<td>4116.36</td>
<td>6</td>
<td>686.059</td>
<td>19.83</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>1690.35</td>
<td>114</td>
<td>14.828</td>
<td>1.89</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>8032.65</td>
<td>1026</td>
<td>7.829</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30806</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.4 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method accounts for a significantly greater percentage of the variance in the data than all other methods.

![Main Effect of METHOD for Prediction of LEFT Hemisphere](image)

Figure B.4 Significant main effect of METHOD trained on the right hemisphere to predict the left in session two.

The main effect of ROI is shown in Figures B.5 and B.6 and these results were investigated using Scheffé post-hoc tests. The Scheffé post-hoc tests show the right hemisphere regions that predict their contra-lateral hemispheres significantly better than other regions at a threshold of alpha equal to 0.05. The insula is significantly different from BA17, BA18,
AC, calc, entorhinal, f inf orb, f mid orb, f sup orb, fus, hipp, olf, f orb/BA47, parahipp, post cing and temp pole. The amygdala is significantly different from BA17, AC, calc, entorhinal, f inf orb, f mid orb, f sup orb, hipp, olf, parahipp, post cing and temp pole. The middle cingulate is significantly different from BA17, f mid orb, f sup orb, olf, parahipp, post cing and temp pole.

**Figure B.5** Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two.  

**Figure B.6** Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two.
B.2 Olfaction Data from Session Three

B.2.1 Left to Predict Right Hemisphere in Session Three

The ANOVA results for olfactory data, session three, training on the data from the left hemisphere and testing on data from the right, are shown in Table B.3.

Table B.3 ANOVA for Olfaction Data, Session Three, Left Hemisphere Predicting Right

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>1222.4</td>
<td>19</td>
<td>64.34</td>
<td>0.98</td>
<td>0.481</td>
</tr>
<tr>
<td>Method</td>
<td>2466.4</td>
<td>6</td>
<td>411.07</td>
<td>5.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>989.1</td>
<td>114</td>
<td>8.676</td>
<td>1.03</td>
<td>0.4081</td>
</tr>
<tr>
<td>Error</td>
<td>8663.1</td>
<td>1026</td>
<td>8.444</td>
<td>8.444</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33807.4</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.7 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method accounts for a significantly greater percentage of the variance in the data than all other methods.

Figure B.7 Significant main effect of METHOD trained on the left hemisphere to predict the right in session three.
B.2.2 Right to Predict Left Hemisphere in Session Three

The ANOVA results for olfactory data, session three, training on the data from the right hemisphere and testing on data from the left, are shown in Table B.4.

**Table B.4** ANOVA for Olfaction Data, Session Three, Right Hemisphere Predicting Left

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>1810.1</td>
<td>19</td>
<td>95.268</td>
<td>1.17</td>
<td>0.2919</td>
</tr>
<tr>
<td>Method</td>
<td>2324</td>
<td>6</td>
<td>387.331</td>
<td>5.38</td>
<td>0.0002</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>1562.4</td>
<td>114</td>
<td>13.705</td>
<td>1.4</td>
<td>0.0054</td>
</tr>
<tr>
<td>Error</td>
<td>10055.7</td>
<td>1026</td>
<td>9.8014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>41457</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.8 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method does not significantly differ from the FLOBS method; however, it accounts for a significantly greater percentage of the variance in the data than the other five methods.

**Figure B.8** Significant main effect of METHOD trained on the right hemisphere to predict the left in session three.
B.3 Olfaction Data from Session Four

B.3.1 Left to Predict Right Hemisphere in Session Four

The ANOVA results for olfactory data, session four, training on the data from the left hemisphere and testing on data from the right, are shown in Table B.5.

Table B.5 ANOVA for Olfaction Data, Session Three, Left Hemisphere Predicting Right

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>722.6</td>
<td>19</td>
<td>38.034</td>
<td>1.21</td>
<td>0.2557</td>
</tr>
<tr>
<td>Method</td>
<td>2948</td>
<td>6</td>
<td>491.33</td>
<td>9.67</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>1212.4</td>
<td>114</td>
<td>10.636</td>
<td>1.46</td>
<td>0.0019</td>
</tr>
<tr>
<td>Error</td>
<td>7462</td>
<td>1026</td>
<td>7.273</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24374.8</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.9 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method accounts for a significantly greater percentage of the variance in the data than all other methods.

Figure B.9 Significant main effect of METHOD trained on the left hemisphere to predict the right in session four.
B.3.2 Right to Predict Left Hemisphere in Session Four

The ANOVA results for olfactory data, session four, training on the data from the right hemisphere and testing on data from the left, are shown in Table B.6.

Table B.6 ANOVA for Olfaction Data, Session Four, Right Hemisphere Predicting Left

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>988.6</td>
<td>19</td>
<td>52.034</td>
<td>1.3</td>
<td>0.1902</td>
</tr>
<tr>
<td>Method</td>
<td>2463.5</td>
<td>6</td>
<td>410.581</td>
<td>8.23</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>1244.2</td>
<td>114</td>
<td>10.914</td>
<td>1.39</td>
<td>0.006</td>
</tr>
<tr>
<td>Error</td>
<td>8044.3</td>
<td>1026</td>
<td>7.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27090.7</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The main effect of method is shown in Figure B.10 and these results were investigated using Scheffé post-hoc tests. Scheffé tests with an alpha equal to 0.05 show that the Kalman method accounts for a significantly greater percentage of the variance in the data than the other methods.

Figure B.10 Significant main effect of METHOD trained on the right hemisphere to predict the left in session four.
B.4 Estimated Decay and Model Comparison

The following is the reanalysis of the model comparisons on the second olfactory session of data. This reanalysis includes the Kalman filter model with the exponential term.

B.4.1 Left to Predict Right Hemisphere

Table B.7 ANOVA for Olfaction Data, Session Two, Left Hemisphere Predicting Right, Including Decay

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>2030.6</td>
<td>19</td>
<td>106.876</td>
<td>1.93</td>
<td>0.0145</td>
</tr>
<tr>
<td>Method</td>
<td>4329.9</td>
<td>7</td>
<td>618.564</td>
<td>14.75</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>2427.3</td>
<td>133</td>
<td>18.251</td>
<td>1.96</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>11153.5</td>
<td>1197</td>
<td>9.318</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>38116.1</td>
<td>1599</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Main Effect of METHOD for Prediction of Right Hemisphere

![Main Effect of METHOD for Prediction of Right Hemisphere]

Figure B.11 Significant main effect of METHOD trained on the left hemisphere to predict the right in session two, including the decay model.
Main effect of ROI for Prediction of Right Hemisphere

**Figure B.12** Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two, including the decay model.

Main Effect of ROI for Prediction of Right Hemisphere

**Figure B.13** Main Effect of ROI trained in the left hemisphere and tested on the right for data from session two, including the decay model.

Interaction of ROI and METHOD on the second run

**Figure B.14** Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.

Interaction of ROI and METHOD on the second run

**Figure B.15** Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.
Figure B.16 Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.

Figure B.17 Significant interaction of METHOD and ROI trained on the left hemisphere to predict the right in session two, including the decay model.
B.4.2 Right to Predict Left Hemisphere

Table B.8 ANOVA for Olfaction Data, Session Two, Right Hemisphere Predicting Left, Including Decay

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>dof</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>3439.3</td>
<td>19</td>
<td>181.017</td>
<td>2.79</td>
<td>0.0002</td>
</tr>
<tr>
<td>Method</td>
<td>5558.2</td>
<td>7</td>
<td>794.025</td>
<td>20.67</td>
<td>0</td>
</tr>
<tr>
<td>ROI*Method</td>
<td>2526.9</td>
<td>133</td>
<td>18.999</td>
<td>2.16</td>
<td>0</td>
</tr>
<tr>
<td>Error</td>
<td>10528.9</td>
<td>1197</td>
<td>8.796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40270.1</td>
<td>1599</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure B.18 Significant main effect of METHOD trained on the right hemisphere to predict the left in session one, including the decay model.
Figure B.19  Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two, including the decay model.

Figure B.20  Main Effect of ROI trained in the right hemisphere and tested on the left for data from session two, including the decay model.

Figure B.21  Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.

Figure B.22  Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.
Figure B.23  Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.

Figure B.24  Significant interaction of METHOD and ROI trained on the right hemisphere to predict the left in session two, including the decay model.
APPENDIX C

REGION OF INTEREST MASKS

Regions of interest were automatically generated from the Talairach Deamon [61][57] using the WFUPickAtlas program[62]. This program provides an easy interface to the Talairach atlas and the AAL atlas[63].

Figure C.1 Amygdala region of interest.

Figure C.2 Anterior cingulate region of interest.
Figure C.3  Brodmann Area 17 region of interest.

Figure C.4  Brodmann area 18 region of interest.

Figure C.5  Calcarine fissure region of interest.
Figure C.6 Entorhinal region of interest.

Figure C.7 Inferior frontal orbit region of interest.

Figure C.8 Middle frontal orbit region of interest.
Figure C.9  Superior frontal orbit region of interest.

Figure C.10  Fusiform region of interest.

Figure C.11  Hippocampus region of interest.
Figure C.12  Insula region of interest.

Figure C.13  Middle cingulate region of interest.

Figure C.14  Olfactory cortex region of interest.
Figure C.15  The union of orbital frontal and Brodmann area 47 region of interest.

Figure C.16  Parahippocampal region of interest.

Figure C.17  Piriform region of interest.
Figure C.18  Posterior cingulate region of interest.

Figure C.19  Superior temporal pole region of interest.

Figure C.20  Thalamus region of interest.
APPENDIX D

PROGRAMS USED IN THIS EXPERIMENT

The following is a list of MatLab and Labview programs used in this experiment. All programs were written by Jason Steffener with the exception of the Main_odorant.presentation.program which was started by Cheuk Ying Tang of Mount Sinai School of Medicine, worked on by Matthias Tabert and William Thomas of Columbia University and also by myself.

work_121004.m This is the program that performs the Kalman filter analysis on all ROIs from a single subject. The program also calculates the percent variance explained by all seven models that are compared in this work, see Section D.1.

kalman_100104.m This is the program that performs the Kalman filter calculations used in work_121004, see Section D.2.

log_like_kahnan_092904.m This programs calculates the log-likelihood of the parameter P, see Section D.3.

log_like_kalman_092904_run.m This program uses the estimate of P to determine the value of sigma squared, see Section D.4.

fit.exponent.m This program finds the parameters of an exponential that best fits to the given data, see Section D.5.

work_122104.m This program performs the analysis of variance across METHOD, ROI, HEMISPHERE and SUBJECT, see Section D.6.

find_sign_posthoc_METHOD This program determines the significant post-hoc tests for the main effect of METHOD, see Section D.7.
find_sign_posthoc_ROI.m This program determines the significant post-hoc tests for the main effect of ROI, see Section D.8.

Assess_Practice_Paced_Breathing This is the Labview program used to train subjects with paced breathing and determine a comfortable breathing rate. The program performs both of these tasks because the breathing pacer can be displayed or hidden, see Section D.8.

Main_odorant_presentation_program This is the main program used during the odorant testing and during the actual fMRI scanning experiment, see Section D.10.

Post-scanning_odorant_assessment_program This is the program used for post-scanning assessment of the odorants, see Section D.11.
D.1 MatLab Program to Perform Kalman Filter Analysis

work_121004

This is the program that performs the Kalman filter analysis on all ROIs from a single subject. The program also calculates the percent variance explained by all seven models that are compared in this work.

%run Kalman filter analyses on mean time courses
clear
close all
runs=1;
path_name='ensure one run through';
while path_name

path_name=uigetdir(pwd,'Select directory of data');
if path_name
    file_names=dir(path_name);
    N=size(file_names,1)-2;  %number of ROI chosen
    P1={};
    for i=3:N+2
        P1{i-2}=fullfile(path_name,file_names(i).name);
    end
    P1=char(P1)
    if P1
        size(P1)
        for i=1:N
            temp=load(P1(i,:))';
            mean_values(i)=mean(temp);  %use mean
                                          %per sig change
            mean_values_of_intro(i)=mean(temp(1:10));
            data(i,:,runs)= (temp-mean_values(i));
        end
        runs=runs+1;
    end
end
end
M=size(data,3);  %number of runs

%%% SET UP DESIGN %%%%%%%%%%%%%%%%%%%%%%%%%
intro_off=10;
on_time=1;
off_time=13;
cycles=5;
design=zeros(intro_off,1);
for i=1:cycles
    design=[design;ones(on_time,1);zeros(off_time,1)];
end
training_design=design-mean(design);
temp=[];
for j=1:M-1
    temp=[temp; training_design];
end
training_design=temp;
analysis_design=[];
for i=2:M
    analysis_design=[analysis_design;design];
end
analysis_design=analysis_design-mean(analysis_design);

%%%%%% SETUP FOR KALMAN FILTER %%%%%%%%%
order=14;
F=eye(order);
    %make sure first and last value of %HRF function don't change from zero
F(1,1)=0;
F(order,order)=0;
This was discussed in Goutte
OPTIONS=[];
OPTIONS=optimset('TolX',0.001);
EST=[];
fullresp=[];
training_start=zeros(order,1);
K_scale_factor=0.01;
Phypo=0.01;
Pupper=10;

%%%% TRAINING %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%-------
[b,a]=butter(3,0.38*2); analysis_start=[]; estimate=[];
N_design=size(design,1);
training_data=[]; %zeros(N_design*(M-1),N);
for i=1:N
    temp=[];
    for j=1:M-1
        temp=[temp;filtfilt(b,a,data(i,:,j))'];
    end
    training_data(:,i)=temp;
    [Pest(i)]=fminbnd(@log_like_kalman_092904,Phypo,...
Pupper,OPTIONS,training_design,training_data(:,i),...
order,training_start,K_scale_factor,F);
    [sigma_sq_est(i)]=log_like_kalman_092904_run...
(Pest(i),training_design,training_data(:,i),order,
training_start, K_scale_factor, F);
[training_state_vector, estimate(i,:), K] = ...
kalman_100104(Pest(i), training_design, ...
training_data(:,i), order, training_start, ...
K_scale_factor, F, sqrt(sigma_sq_est(i)));
analysis_start(:,i) = training_state_vector(:,end);
end

%%%% CREATE KF DESIGN %%%%%%%%%%%%%%%%%%
KF_design = []; for i=1:N
    KF_design_temp = conv(analysis_start(:,i), ... / ...
    sum(analysis_start(:,i)), design);
    KF_design_temp = KF_design_temp(1:length(design));
    % KF_design(:,i) = KF_design_temp / sum(KF_design_temp);
    KF_design(:,1) = KF_design_temp;
end
pl = 'j:\thesis_data';
nl = 'design.mat';
b1 = textread(fullfile(pl, nl), '%s', 'delimiter', '	', '... ...
    'whitespace', '');
design_fsl = read_FSL_design(b1);

%%%% CREATE BLOCK UNCONVOLVED DESIGN %%%%%%%%%%%%
unconvolved_design = zeros(10,1);
for i=1:cycles
    unconvolved_design = [unconvolved_design; ...
        ones(4,1); zeros(10,1)];
end

%%%% CREATE DELAYED BLOCK UNCONVOLVED DESIGN %%%
delayed_block_design = [0; 0; unconvolved_design(1:end-2)];

%%%% CREATE STANDARD DESIGN %%%%%%%%%%%%
RT = 3;
H = jrs_hrf(RT);
standard_design = zeros(10,1);
for i=1:cycles
    standard_design = [standard_design; ones(4,1); ...
        zeros(10,1)];
end
N_standard = length(standard_design);
standard_design = conv(H, standard_design);
standard_design = standard_design(1:N_standard);
standard_design = standard_design - mean(standard_design);

%%%% CREATE GAMMA CONVOLVED DESIGN %%%%%%
H_single_gamma = jrs_hrf(RT, [6 16 1 1 100000 0 32]);
N_standard = length(standard_design);
gamma_design = conv(H_single_gamma, standard_design);
gamma_design = gamma_design(1:N_standard);
gamma_design=gamma_design-mean(gamma_design);

%%% CREATE POELLINGER DESIGN %%%%%%%%
RT=3; H=jrs_hrf(RT); poellinger_design=zeros(10,1);
for i=1:cycles
    poellinger_design=[poellinger_design; ones(2,1);...
                      zeros(12,1)];
end
N_standard=length(poellinger_design);
poellinger_design=conv(H,poellinger_design);
poellinger_design=poellinger_design(1:N_standard);
poellinger_design=poellinger_design-mean(poellinger_design);

%%% CREATE BETA SCORES FOR THE KF DESIGN %%%
for i=1:N
    D=filtfilt(b,a,data(i,:,end));
    Ctemp=corrcoef(KF_design(:,i),D);
    CKF(i)=Ctemp(2);
    CKFresvar(i)=var(D'-KF_design(:,i)*...  
                      pinv(KF_design(:,i))*D');
    Ctemp=corrcoef(design_fsl(:,1),D);
    CFSL(i)=Ctemp(2);
    beta(i)=pinv(KF_design(:,i))*D';
    beta_fsl(i,:)=pinv(design_fsl)*D';
    est_fsl(i,:)=design_fsl*beta_fsl(i,:);
    Ctemp=corrcoef(standard_design,D);
    Cstan(i)=Ctemp(2);
    Cstanresvar(i)=var(D'-standard_design*...  
                      pinv(standard_design)*D');
    Ctemp=corrcoef(unconvolved_design,D);
    Cuncon(i)=Ctemp(2);
    Cunconresvar(i)=var(D'-unconvolved_design*...  
                      pinv(unconvolved_design)*D');
    Ctemp=corrcoef(delayed_block_design,D);
    Cdelay(i)=Ctemp(2);
    Cdelayresvar(i)=var(D'-delayed_block_design*...  
                      pinv(delayed_block_design)*D');
    Ctemp=corrcoef(gamma_design,D);
    Cgamma(i)=Ctemp(2);
    Cgammaresvar(i)=var(D'-gamma_design*...  
                      pinv(gamma_design)*D');
    Ctemp=corrcoef(poellinger_design,D);
    Cpoel(i)=Ctemp(2);
    Cpoelresvar(i)=var(D'-poellinger_design*...
pinv(poellinger_design)*D');
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
data_out_RV=[CFSLresvar; CKFresvar; Cdelayresvar;...
          Cgammaresvar; Cpoelresvar; Cstanresvar; Cunconresvar];

[pl, n1]=fileparts(P1(1,:));
[p2, n2]=fileparts(p1);
[p3,n3]=fileparts(p2);
cd(p3)

eval(['save ' [vis_trans '_ ' num2str(M) ' run2 ']])
D.2 MatLab Program of Kalman Filter Algorithm

This is the program that performs the Kalman filter calculations used in work_121004.

```
function [state_vector, estimate, K]=...
    kalman_100104(P,design, data, order, start,...
    K_scale_factor, F, sigma_est)
pad=zeros(1,order-1);
K=eye(order).*(1/K_scale_factor);
state_vector=start;
N=length(data);
innovation(1)=0.0001;
R(1)=0.0001;
for i=2:N
    Kold=F*K(:,:,i-1)*F'+P;
    R(i)=design(i)*K(i)*design(i)'+1;
    G(i)=inv(R(i));
    est(i)=design(i)*h(i);
    a(i)=data(i)-est(i);
    h(i+1)=G(i)*a(i)+h(i);
    K(i+1)=K(i)-G(i)*R(i)*G(i)'+P;
end
```

D.3 MatLab Program for State Variable Variance Estimate

This programs calculates the log-likelihood of the parameter P.

```
function [output]=log_like_kalman_092004(P, data, design, ...
    start);
K(1)=100; h(1)=start; N=length(data); F=[0 0; 0 1];
for i=1:N
    R(i)=design(i)*K(i)*design(i)'+1;
    G(i)=K(i)*design(i)'*inv(R(i));
    est(i)=design(i)*h(i);
    a(i)=data(i)-est(i);
    h(i+1)=G(i)*a(i)+h(i);
    K(i+1)=K(i)-G(i)*R(i)*G(i)'+P;
end
output=(-N*log(sum((a.^2)/(N.*R)))-0.5*sum(log(R))));
```
D.4 MatLab Program for Measurement Variance Estimate

This program uses the estimate of $P$ from the to determine the value of sigma squared.

```matlab
function [sigma_sq_est]=log_like_kalman_092904_run...
    (P,design,data,order,start,K_scale_factor,F)
pad=zeros(1,order-1);
K=eye(order).*(1/K_scale_factor);
state_vector=start; N=length(data); innovation(1)=0.0001;
R(1)=0.0001;
for i=2:N
    Kold=F*K*F'+P;
    R(i)=[design(i) pad]*Kold* [design(i) pad]'+1;
    gain=F*Kold*[design(i) pad]'*inv(R(i));
    estimate(i)=[design(i) pad]*state_vector(:,i-1);
    innovation(i)=data(i)-estimate(i);
    state_vector(:,i)=F*state_vector(:,i-1)+gain*...
        innovation(i);
    K=Kold-gain*[design(i) pad]*Kold;
    pad=[design(i) pad(1:end-1)];
end
sigma_sq_est=sum((innovation.^2)./(N.*R));
```

D.5 MatLab program for Fitting an Exponential Curve

This program finds the parameters of an exponential that best fits to the given data.

```matlab
function [a,b,c]=fit_exponential(data);
N=length(data);
RT=3;
time=[0:RT:(N-1)*RT]';
F=fitoptions('Method','NonlinearLeastSquares',...
    'Algorithm','Levenberg-Marquardt');
F.StartPoint= [0 0]; F.Display='off';
G=fittype('a*exp(b*x)');
[fittedmodel,goodness]=fit(time,data,G,F); if size(goodness)
    a=fittedmodel.a;  b=fittedmodel.b;
else
    a=0;  b=0;
end
D.6 MatLab Program to Perform Analysis of Variance

This program performs the analysis of variance across METHOD, ROI, HEMISPHERE and SUBJECT.

clear
close all

ROI_names={'BA17';'BA18';'amyg'; 'AC';'calc';...
'entorhinal';'f inf orb';'f mid orb';'f sup orb';...
'fus';'hipp';'ins';'mid cing';'olf';'f orb/BA47';...
'parahipp';'piriform';'post cing';'temp pole'; 'thal'};

method_names=('FLOBS';'Kalman';'Delayed';'Gamma';...
'Poellinger';'Standard';'Stimulus';);

hemi_names={'Left';'Right'};

Gnames={ROI_names;method_names;hemi_names};

N_hemis=length(hemi_names);

N_methods=length(method_names); N_ROI=length(ROI_names);

names='ensure one run through';

subjs=1; data_RV=[]; data_V=[];

while names

%P1=spm_get(Inf,'.txt','Select time courses from ROI');
[names,paths]=uigetfile('*.mat','Select visual data');

if names

temp=load(fullfile(paths,names));
data_RV(:,:,subjs)=temp.data_out_RV;
%data_V(:,subjs)=var(temp.data(:,:,end)');
data_V(:,subjs)=var([temp.data(:,:,2)';
temp.data(:,:,3)';
temp.data(:,:,4)']);%%%%%%CAREFUL HERE
subjs=subjs+1;

end

%create var of res after GLM

N_subjs=subjs-1;

hemis_col=[];

for i=1:N_subjs*N_ROI*N_methods

hemis_col=[hemis_col; hemi_names];

end

ROI_col=[];

for i=1:N_subjs*N_methods
for j=1:N_ROI
    for k=1:N_hemis
        ROI_col=[ROI_col; ROI_names(j)];
    end
end

methods_col=[];
for i=1:N_subjs
    for j=1:N_methods
        for k=1:N_ROI*N_hemis
            methods_col=[methods_col; method_names(j)];
        end
    end
end

D=[];
for i=1:N_subjs
    for j=1:N_methods
        for k=1:N_ROI*N_hemis
            D=[D; (1-(data_RV(j,:,i)'./data_V(:,i)))*100];
        end
    end
end

subjs_col=[];
for i=1:N_subjs
    for j=1: N_hemis*N_ROI*N_methods;
        subjs_col((i-1)*N_hemis*N_ROI*N_methods+j,1)=(i);
    end
end

[pvals,tbl,stats] = anovan(D, { subjs_col ROI_col ... methods_col hemis_col},'model',2,'random', ... [1],’varnames’,{ ‘subjs’ ‘ROI’ ‘Method’ ‘Hemisphere’});

%create bar plot of METHOD
[c, m, h]=multcompare(stats,’dim’, [3],’ctype’,’scheffe’);
out=find_sign_posthoc_METHOD(c,D,method_names,methods_col)
figure(15);
clf h=axes; hold on
barh([1:7],m(1:7,1));
set(h,’Ytick’,[1:7]) set(h,’Yticklabel’,method_names(:))
for i=1:7
    h2=line([m(i,1)-m(i,2), m(i,1)+m(i,2)], [i,i]);
    set(h2,’Color’,’r’)
end
xlabel(’Percent Variance Explained’)
axis([0 60 0.5 7.5])
%axis tight

%create bar plot of ROI
[c, m, h]=multcompare(stats,'dim', [2], 'ctype', 'scheffe');
find_sign_posthoc_ROI(c,m,D,ROI_names,ROI_col)
figure(6); clf;
h=axes; hold on
barh([1:10],m(1:10,1));
set(h,'Ytick', [1:10])
set(h,'Yticklabel',ROI_names(1:10))
for i=1:10
    h2=line([m(i,1)-m(i,2), m(i,1)+m(i,2)],[i,i]);
    set(h2,'Color','r')
end
xlabel('Percent Variance Explained')
axis([0 60 0.5 10.5])

figure(7);
clf
h=axes;
hold on
barh([1:10],m(11:20,1));
set(h,'Ytick', [1:10])
set(h,'Yticklabel',ROI_names(11:20))
for i=1:10
    h2=line([m(i+10,1)-m(i+10,2), m(i+10,1)+m(i+10,2)],[i,i]);
    set(h2,'Color','r')
end
xlabel('Percent Variance Explained')
axis([0 60 0.5 10.5])

figure(8); clf h=axes; hold on
barh([1:2],m(1:2,1));
set(h,'Ytick', [1:2])
set(h,'Yticklabel',hemi_names(1:2))
for i=1:2
    h2=line([m(i,1)-m(i,2), m(i,1)+m(i,2)],[i,i]);
    set(h2,'Color','r')
end
xlabel('Percent Variance Explained')
axis([0 60 0.5 2.5])
title('Main Effect of HEMISPHERE tested on the second run')

[c, m, h]=multcompare(stats,'dim', [2 4], 'ctype', 'scheffe');
outROIHEM=find_signposthoc_intROI_HEMI(c,ROI_n,ROI_col,D)
M1=[];
M2=[]; for i=1:20
    M1(i,1)=m(i,1);
    M1(i,2)=m(i+20,1);
    M2(i,1)=m(i,2);
    M2(i,2)=m(i+20,2);
end
figure(9)
clear
h=axes;
hold on
barh([1:10],M1(1:10,:),')group');
set(h,'Ytick',[1:10]) set(h,'Yticklabel',ROI_names(1:10))
for i=1:10
    h2=line([M1(i,1)-M2(i,1),M1(i,1)+M2(i,1)],[i-0.15,i-0.15]);
    set(h2,'Color','r')
    h2=line([M1(i,2)-M2(i,2),M1(i,2)+M2(i,2)],[i+0.15,i+0.15]);
    set(h2,'Color','r')
end
xlabel('Per Var Explained')
axis([0 60 0.5 10.5])
title('Inter of ROI and Hemi on the second run')

figure(10)
clear
h=axes;
hold on
barh([1:10],M1(11:20,:),')group');
set(h,'Ytick',[1:10])
set(h,'Yticklabel',ROI_names(11:20))
for i=1:10
    h2=line([M1(i+10,1)-M2(i+10,1),M1(i+10,1)+M2(i+10,1)],[i-.15,i-.15]);
    set(h2,'Color','r')
    h2=line([M1(i+10,2)-M2(i+10,2),M1(i+10,2)+M2(i+10,2)],[i+.15,i+.15]);
    set(h2,'Color','r')
end
xlabel('Percent Variance Explained') axis([0 60 0.5 10.5])
title('Interaction of ROI and Hemisphere on the third run')
legend('Left','Right')
output=find_sign_posthoc_intROI_HEMI(c,ROI_names,ROI_col,D)

%%% BAR PLOTS FOR METHOD/ROI %%%%%%%%%%%%%%%%%%%%%%%%%
[c, m, h]=multcompare(stats,'dim', [2 3], 'ctype', 'scheffe');
M1=[];
M2=[]; for i=1:20
  M1(i,1)=m(i,1);
  M1(i,2)=m(i+20,1);
  M1(i,3)=m(i+40,1);
  M1(i,4)=m(i+60,1);
  M1(i,5)=m(i+80,1);
  M1(i,6)=m(i+100,1);
  M1(i,7)=m(i+120,1);
  M2(i,1)=m(i,2);
  M2(i,2)=m(i+20,2);
  M2(i,3)=m(i+40,2);
  M2(i,4)=m(i+60,2);
  M2(i,5)=m(i+80,2);
  M2(i,6)=m(i+100,2);
  M2(i,7)=m(i+120,2);
end
figure(11)
clf
h=axes;
hold on
barh([1:5],M1(1:5,:),'group');
set(h,'Ytick',[1:5])
set(h,'Yticklabel',ROI_names(1:5))
for i=1:5
  h2=line([M1(i,1)-M2(i,1), M1(i,1)+M2(i,1)],...
          [i-0.35,i-0.35]); set(h2,'Color','r')
  h2=line([M1(i,2)-M2(i,2), M1(i,2)+M2(i,2)],...
          [i-0.225,i-0.225]); set(h2,'Color','r')
  h2=line([M1(i,3)-M2(i,3), M1(i,3)+M2(i,3)],...
          [i-0.115,i-0.115]); set(h2,'Color','r')
  h2=line([M1(i,4)-M2(i,4), M1(i,4)+M2(i,4)],...
          [i+0,i+0]); set(h2,'Color','r')
  h2=line([M1(i,5)-M2(i,5), M1(i,5)+M2(i,5)],...
          [i+0.115,i+0.115]); set(h2,'Color','r')
  h2=line([M1(i,6)-M2(i,6), M1(i,6)+M2(i,6)],...
% Interaction of ROI and METHOD on the second run

xlabel('Percent Variance Explained')
axis([0 60 0.5 5.5])
title('Interaction of ROI and METHOD on the second run')

figure(12)
cf
h=axes;
hold on
barh([6:10],M1(6:10,:),'group');
set(h,'Ytick',[6:10])
set(h,'Yticklabel',ROI_names(6:10))
for i=6:10
    h2=line([M1(i,1)-M2(i,1), M1(i,1)+M2(i,1)],
             [i-0.35,i-0.35]); set(h2,'Color','r')
    h2=line([M1(i,2)-M2(i,2), M1(i,2)+M2(i,2)],
             [i-0.225,i-0.225]); set(h2,'Color','r')
    h2=line([M1(i,3)-M2(i,3), M1(i,3)+M2(i,3)],
             [i-0.115,i-0.115]); set(h2,'Color','r')
    h2=line([M1(i,4)-M2(i,4), M1(i,4)+M2(i,4)],
             [i+0,i+0]); set(h2,'Color','r')
    h2=line([M1(i,5)-M2(i,5), M1(i,5)+M2(i,5)],
             [i+0.115,i+0.115]); set(h2,'Color','r')
    h2=line([M1(i,6)-M2(i,6), M1(i,6)+M2(i,6)],
             [i+0.225,i+0.225]); set(h2,'Color','r')
    h2=line([M1(i,7)-M2(i,7), M1(i,7)+M2(i,7)],
             [i+0.35,i+0.35]); set(h2,'Color','r')
end

xlabel('Percent Variance Explained')
axis([0 60 5.5 10.5])
title('Interaction of ROI and METHOD on the second run')

% legend(method_names)
figure(13)
clf
h=axes;
hold on
barh([11:15],M1(11:15,:),'group');
set(h,'Ytick',[11:15])
set(h,'Yticklabel',ROI_names(11:15))
for i=11:15
    h2=line([M1(i,1)-M2(i,1), M1(i,1)+M2(i,1)],
             [i-0.35,i-0.35]); set(h2,'Color','r')
end
h2=line([M1(i,2)-M2(i,2), M1(i,2)+M2(i,2)],...
   [i-0.225,i-0.225]); set(h2,'Color','r')
h2=line([M1(i,3)-M2(i,3), M1(i,3)+M2(i,3)],...
   [i-0.115,i-0.115]); set(h2,'Color','r')
h2=line([M1(i,4)-M2(i,4), M1(i,4)+M2(i,4)],...
   [i+0,i+0]); set(h2,'Color','r')
h2=line([M1(i,5)-M2(i,5), M1(i,5)+M2(i,5)],...
   [i+0.115,i+0.115]); set(h2,'Color','r')
h2=line([M1(i,6)-M2(i,6), M1(i,6)+M2(i,6)],...
   [i+0.225,i+0.225]); set(h2,'Color','r')
h2=line([M1(i,7)-M2(i,7), M1(i,7)+M2(i,7)],...
   [i+0.35,i+0.35]); set(h2,'Color','r')
end
xlabel('Percent Variance Explained')
axis([0 60 10.5 15.5])
title('Interaction of ROI and METHOD on the second run')

figure(14)
cclf
h=axes;
hold on
barh([16:20],M1(16:20,:),'group');
set(h,'Ytick',[16:20])
set(h,'Yticklabel',ROI_names(16:20))
for i=16:20
h2=line([M1(i,1)-M2(i,1), M1(i,1)+M2(i,1)],...
   [i-0.35,i-0.35]); set(h2,'Color','r')
h2=line([M1(i,2)-M2(i,2), M1(i,2)+M2(i,2)],...
   [i-0.225,i-0.225]); set(h2,'Color','r')
h2=line([M1(i,3)-M2(i,3), M1(i,3)+M2(i,3)],...
   [i-0.115,i-0.115]); set(h2,'Color','r')
h2=line([M1(i,4)-M2(i,4), M1(i,4)+M2(i,4)],...
   [i+0,i+0]); set(h2,'Color','r')
h2=line([M1(i,5)-M2(i,5), M1(i,5)+M2(i,5)],...
   [i+0.115,i+0.115]); set(h2,'Color','r')
h2=line([M1(i,6)-M2(i,6), M1(i,6)+M2(i,6)],...
   [i+0.225,i+0.225]); set(h2,'Color','r')
h2=line([M1(i,7)-M2(i,7), M1(i,7)+M2(i,7)],...
   [i+0.35,i+0.35]); set(h2,'Color','r')
end
xlabel('Percent Variance Explained')
axis([0 60 15.5 20.5])
title('Interaction of ROI and METHOD on the second run')
%legend(method_names)

% group1_name='Kalman';
% temp_group1=strfind(methods_col,group1_name);
% group1=[];
% group_combined={};
% for i=1:length(temp_group1)
%     if temp_groupl{i}
%         group1=[group1; i];
%     end
% end
% sub_hemi=hemis_col(group1);
% sub_ROI=ROI_col(group1);
% sub_subjs=subjs_col(group1);

[pvals,tbl,stats] = anovan(D(group1), {sub_subjs sub_ROI sub_hemi}, 'model',2,'random', [1], 'varnames',... 
{ 'subjs' 'ROI' 'Hemisphere'});

[c, m, h]=multcompare(stats,'dimension', [2],...
'ctype','scheffe');

figure(6); clf h=axes; hold on
barh([1:10],m(1:10,1));
set(h,'Ytick',[1:10])
set(h,'Yticklabel',ROI_names(1:10))
for i=1:10
    h2=line([m(i,1)-m(i,2), m(i,1)+m(i,2)], [i,i]);
    set(h2,'Color','r')
end xlabel('Percent Variance Explained')
axis([0 60 0.5 10.5])
title('ME of ROI tested on the 3rd run in the Kalman')

figure(7);
clf
h=axes;
hold on
barh([1:10],m(11:20,1));
set(h,'Ytick',[1:10])
set(h,'Yticklabel',ROI_names(11:20))
for i=1:10
    h2=line([m(i+10,1)-m(i+10,2), m(i+10,1)+m(i+10,2)],... 
        [i,i]);
    set(h2,'Color','r')
end xlabel('Percent Variance Explained')
axis([0 60 0.5 10.5])
title('ME of ROI tested on the 4th run in the Kalman')

find_sign_posthoc_ROI(c,m,D,ROI_names,ROI_col)

```
group1_name='Kalman'; group2_name='Standard';
temp_group1=strfind(methods_col,group1_name);
group1=[];
group_combined={};
for i=1:length(temp_group1)
    if temp_group1{i}
        group1=[group1; i];
    end
end

temp_group2=strfind(methods_col,group2_name);
group2=[];
for i=1:length(temp_group2)
    if temp_group2{i}
        group2=[group2; i];
    end
end
for i=1:length(group1)
    group_combined(i,1)=group1_name;
end
for i=length(group1)+1:length(group1)+length(group2)
    group_combined(i,1)=group2_name;
end

sub_data=[D(group1); D(group2)]; [p, table, stats_ANOVA1]=anovall(sub_data, group_combined)
```
D.8 MatLab Program to Perform Post-Hoc Analyses for Main Effect of ROI

This program determines the significant post-hoc tests for the main effect of ROI.

function find_sign_posthoc_ROI(c,m,D,ROI_names,ROI_col)

m_max=max(m(:,1));
max_ROI=find(m(:,1)==m_max);
ROI_names(max_ROI);
N1=size(c,1);
F=find((c(:,3)>0)||(c(:,5)<0));
N2=length(F);
for i=1:N2
    cout(i,1)=c(F(i),1);
    cout(i,2)=c(F(i),2);
end
F1=(find(cout(:,1)==max_ROI));
F2=(find(cout(:,2)==max_ROI));
diff_from=[cout(F2,1); cout(F1,2)];
ROI_names(max_ROI)
disp('is sign. different from') char(ROI_names(diff_from))

m_minus_max1=m; m_minus_max1(max_ROI,:)=[0 0]; m=m_minus_max1;
m_max=max(m(:,1));
max_ROI=find(m(:,1)==m_max);
ROI_names(max_ROI);
N1=size(c,1);
F=find((c(:,3)>0)||(c(:,5)<0));
N2=length(F);
for i=1:N2
    cout(i,1)=c(F(i),1);
    cout(i,2)=c(F(i),2);
end
F1=(find(cout(:,1)==max_ROI));
F2=(find(cout(:,2)==max_ROI));
diff_from=[cout(F2,1); cout(F1,2)];
ROI_names(max_ROI) disp('is sign. different from')
char(ROI_names(diff_from))

m_minus_max1=m;
m_minus_max1(max_ROI,:)=[0 0]; m=m_minus_max1;
m_max=max(m(:,1));
max_ROI = find(m(:,1) == m_max);
ROI_names(max_ROI);
N1 = size(c,1);
F = find((c(:,3) > 0) | (c(:,5) < 0));
N2 = length(F);
for i = 1:N2
    cout(i,1) = c(F(i),1);
    cout(i,2) = c(F(i),2);
end
F1 = (find(cout(:,1) == max_ROI));
F2 = (find(cout(:,2) == max_ROI));
diff_from = [cout(F2,1); cout(F1,2)];
ROI_names(diff_from);
ROI_names(max_ROI)
disp('is sign. different from')
char(ROI_names(diff_from))
D.9 LabView Program to Assess Paced Breathing

This LabView program was used to train subjects with paced breathing and determine a comfortable breathing rate. Figures D.1 and D.2 show the front panel and Figure D.3 shows the block diagram.

**Figure D.1** LabView front panel of the program used to familiarize subjects with paced breathing. The left hand side is what the experimenter sees, and the right is what the subject sees.

**Figure D.2** LabView front panel of the program used to familiarize subjects with paced breathing. The left hand side is what the experimenter sees, and the right is what the subject sees.
Figure D.3 LabView wiring diagram of the program used to familiarize subjects with paced breathing.
D.10 LabView Program to Control Olfactometer

The main program used during the odorant testing and during the actual fMRI scanning experiment. Figure D.4 shows the front panel.

**Figure D.4** LabView front panel of the main odorant presentation program used during scanning. The left hand side is what the experimenter sees, and the right is what the subject sees. Note that the subject sees exactly the same screen as they did during practice.
Figure D.5 LabView wiring diagram of the main odorant presentation program used during scanning. Note that most of the events of this program occur in the 40 frame sequence structure. The first four frames of this are shown in the following figures.
**Figure D.6** First frame of the sequence in the main odorant presentation program. This frame delivers the baseline clear air to the subject.

**Figure D.7** Second frame of the sequence in the main odorant presentation program. This frame delivers the first odorant to the subject.
Figure D.8  Third frame of the sequence in the main odorant presentation program. This frame delivers clear air to the subject after an odorant was presented.

Figure D.9  The frame of the sequence which saves all behavioral data to a text file at the completion of the experiment.
D.11 LabView Program for Post-Scanning Assessment of Odorants

This is the program used for post-scanning assessment of the odorants.

Figure D.10 LabView front panel of the post-scanning odorant assessment program. This program is used to readminister the odorants to the subjects and request behavioral feedback, all of which is displayed on this screen. What the subjects sees is projected on a separate screen and is shown in the following figures.
Figure D.11  LabView wiring diagram of the post-scanning odorant assessment program. The diagram is split and the top figure is the left hand side of the diagram and the bottom shows the right hand side.
Figure D.12  LabView front panel of the sub program of post-scanning odorant assessment program used to present the odorants and record subject perceptions. This is a computerized version of the post-scanning odorant assessment protocol of Cerf-Ducastel and Murphy 2004 [64].

Figure D.13  LabView front panel of the sub program of post-scanning odorant assessment program used to rate the pleasantness of the odorant.
Figure D.14  LabView wiring diagram of the sub program of post-scanning odorant assessment program used to present the odorants and record subject perceptions, as shown in Figure D.12.

Figure D.15  LabView wiring diagram of the sub program of post-scanning odorant assessment program used to rate the pleasantness of the odorant, as shown in Figure D.13.
Figure D.16 LabView front panel of the odorant intensity rating scale.
D.12 LabView Program used to Deliver Visual Stimuli

This is the LabView program used to deliver the sustained and transient flickering checkboard stimuli. The timing parameters are all adjustable allowing it the flexibility to perform in a variety of experimental situations. The program again uses the split screen concept, so that subject only sees the checkerboard and the experimenter only sees the controls.

Figure D.17 LabView front panel of the main odorant presentation program used during scanning. The top is what the experimenter sees, and the bottom is what the subject sees. Note that the subject sees exactly the same screen as they did during practice.
Figure D.18  LabView front panel of the main odorant presentation program used during scanning. The left hand side is what the experimenter sees, and the right is what the subject sees. Note that the subject sees exactly the same screen as they did during practice.
REFERENCES


