



**A Comparison of Neuroimaging Software and a Contour  
Inference Method for analysis of Task-fMRI data**

by

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## Declarations

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I, Alexander Bowring, hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in these, or any other Universities. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration, except where specifically indicated in the text.

- The work presented in Chapter 3 has been published in the *NeuroImage* journal (Bowring et al., 2018). This work was presented at the *Organization for Human Brain Mapping* (OHBM) Annual Meetings in 2017 and 2018. At the OHBM 2018 Annual Meeting, this work was the recipient of an oral presentation and Merit Abstract Award.
- The work presented in Chapter 4 has been published in the *NeuroImage* journal (Bowring et al., 2018). This work was presented at the OHBM Annual Meeting in 2017, where it was the recipient of an oral presentation.
- The work presented in Chapter 5 is based on a pre-printed manuscript.

Alexander Bowring

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## Abstract

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Over the last three decades, Functional Magnetic Resonance Imaging (fMRI) has rapidly progressed to become the primary tool for human brain mapping. Recently however, considerable attention within the field has been directed towards data-sharing and open science initiatives. This has been driven by a growing apprehension about the reproducibility of findings within the neuroimaging literature, amid concerns that current inference procedures are often misused or misinterpreted such that the overall scientific conclusions become distorted. One aspect specific to neuroimaging pinpointed as a cause for poor reproducibility is the high flexibility of a typical fMRI workflow. In the first part of this thesis, we investigate how the choice of software package used to conduct a statistical analysis can influence the group-level results of a task-fMRI study. We use publicly shared data from three published task-fMRI studies, and reanalyze each study within the three main neuroimaging software packages, AFNI, FSL and SPM, using parametric and nonparametric inference. All information on how to process, analyze, and model each dataset we obtain from the publications. We use a variety of quantitative and qualitative comparison methods to gauge the scale of variability in our results and assess fundamental differences between each software package. While qualitatively we find broad similarities between packages, we also discover marked differences, such as Dice similarity coefficient values ranging from 0.000 to 0.743 in comparisons of thresholded statistic maps between software. We discuss the challenges involved in our replication attempt, while also utilizing open science tools in an effort to make our own research reproducible. In the second part of this thesis, we extend a contour inference method initially proposed by *Sommerfeld, Sain, and Schwartzman (2018) (SSS)* to develop spatial confidence sets (CSs) on clusters found in thresholded blood-oxygen-level dependent (BOLD) effect size maps. While traditional inferences based on hypothesis testing indicate where the null, i.e. an effect size of zero, can be rejected, the CSs give statements about where effect sizes exceed a *positive* threshold analogous to confidence intervals simultaneously across the entire brain. We make advancements to theoretical aspects and implementation of contour inference to improve the method's finite-sample performance. We extend the wild bootstrap theory presented in SSS, proposing a method based on the t-bootstrap, and recommend that the bootstrapped residuals are multiplied by Rademacher variables instead of Gaussian variables. We also develop a linear interpolation method for computing the topological boundary over which the bootstrap is applied. Notably, we demonstrate that

the framework used in SSS for assessing simulations manifests considerable positive bias in the simulation results, and propose our own novel construction to solve this issue. In the final part of this thesis, we make further theoretical developments to contour inference so that the method can operate on the Cohen's  $d$  and partial  $R^2$  effect sizes commonly reported at the end of a neuroimaging study. For the second and third parts of this thesis, we carry out intensive Monte Carlo simulations on synthetic 3D data to investigate the accuracy of contour inference on signals representative of fMRI activation clusters. We also demonstrate the method on two 'big' fMRI datasets, obtaining confidence sets to localize activation in functional data from the Human Connectome Project and UK Biobank.



# CHAPTER 1

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## Introduction

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Since its inception at the end of the twentieth century, functional Magnetic Resonance Imaging (fMRI) has experienced a meteoric rise to become the primary tool for human brain mapping. While many forms of the technique exist, introduction of the particular method based on the Blood Oxygenization Level Dependant (BOLD) effect has ultimately proven to be the catalyst in elevating fMRI to such stature within the neuroimaging community. Taking advantage of the magnetic properties of oxygen-rich red blood cells, BOLD fMRI measures changes in blood oxygenization alongside cerebral blood flow and volume as a proxy to identify brain areas where elevated neuronal activity has occurred in response to a stimulus. While the relationship between the BOLD effect and neuronal activity is complex and remains controversial, it is the unique attributes of BOLD fMRI – in particular, its capacity for non-invasive recording of signals across the entire brain at a high spatial resolution – that set the technique apart from other scanning methods.

However, BOLD fMRI is also a *noisy* process. The MR signal researchers set out to measure during a scanning session is corrupted by artefacts from both the imaging hardware and the physiology of the participant. Examples of scanner noise include inhomogeneities of the magnetic field that can cause spatial distortion or blurring in the MR image, and scanner drift characterized by temporal degradation of the signal. Physiological noise induced by subject motion, respiration, and heart-beat exacerbate the problem.

Because of the low signal-to-noise, researchers must apply a series of statistical techniques to find meaning in the data. This usually entails carrying out a number of preprocessing, modelling and analysis steps which together constitute the fMRI processing pipeline. The fundamental objectives of preprocessing are to standardize brain locations across participants, to apply methods ensuring that the data conform to statistical assumptions required for analysis, and to reduce the influence of the

aforementioned noise artefacts present in the data. This is achieved by conducting a number of steps, including slice-timing correction, motion correction, normalization, registration of the functional data to an anatomical template, and spatial smoothing.

For task-based fMRI, a mass-univariate approach is utilized to model the data. During the scanning session, functional data are acquired in the form of voxels – cubic intensity units that partition the brain comparable to the way in which pixels partition a computer screen. Each voxel's time-series is considered independently within the general linear model framework as a combination of signal components. To evaluate the effect of an experimental task condition relative to a baseline condition, hypothesis testing is performed at each voxel to compute a statistical parametric map of  $t$ -statistic values. Here, the behaviour of the signal under the null hypothesis of no activation is estimated using either a parametric approach, appealing to the body of mathematics known as Random Field Theory, or a non-parametric approach, where permutation-methods are applied to estimate the null-distribution directly from the data. Finally, the statistical parametric map is thresholded to localize brain function.

While we have provided a brief overview of the fMRI analysis pipeline, it is notable that there is not a general consensus as to how each particular analysis step should be carried out. Consequently, researchers have the freedom to make many choices during an analysis, such as how much smoothing is applied to the data, or how the hemodynamic response of blood flow to active neuronal tissues is modelled. However, this 'methodological plurality' comes with a drawback. While conceptually similar, two different analysis pipelines applied on the same dataset may not produce the same results. In perhaps the most comprehensive study on this topic (Carp, 2012, Plurality...), a single publicly available fMRI dataset was analyzed using over 6,000 unique analysis pipelines, generating 34,560 unique thresholded activation images. These results displayed a substantial degree of flexibility in both the sizes and locations of significant clusters. Further differences in methods, implementations across software packages, operating systems and even software versions can contribute to variability in the final scientific outcomes (add refs).

The problem is, with so many statistically valid methodological strategies available, if you try them all you are likely to find *something*. The high analytic flexibility associated to fMRI has therefore been pinpointed as a key risk factor for inflated false positive results (Ioannidis, 2005, why most research findings are false). This may also be compounded by publication bias, for which there has been evidence to suggest that studies finding a significant effect are disproportionately represented within the fMRI literature.

### 2.1 The Study of Brain Function

### 2.2 Magnetic Resonance Imagery (MRI)

### 2.3 Task-based functional Magnetic Resonance Imagery (t-fMRI)

#### 2.3.1 Overview

#### 2.3.2 Pre-processing

#### 2.3.3 Statistical Analysis: Subject-level

#### 2.3.4 Statistical Analysis: Group-level

### 2.4 Neuroimaging Software Packages

#### 2.4.1 SPM

#### 2.4.2 FSL

#### 2.4.3 AFNI

### 2.5 Reproducibility of fMRI Results

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### Exploring the Impact of Analysis Software on Task-fMRI Results

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#### **3.1 Data and Analysis Methods**

##### **3.1.1 Study Description and Data Source**

##### **3.1.2 Data Analyses**

##### **3.1.3 Comparison Methods**

##### **3.1.4 Permutation Test Methods**

#### **3.2 Results**

##### **3.2.1 Cross-Software Variability for Parametric Inference**

##### **3.2.2 Cross-Software Variability for Non-Parametric Inference**

##### **3.2.3 Intra-Software Variability, Parametric vs Non-Parametric**

#### **3.3 Reproducibility**

##### **3.3.1 Scripting of Analysis and Figures**

##### **3.3.2 Results Sharing**

#### **3.4 Discussion**

##### **3.4.1 Limitations**

#### **3.5 Conclusion**



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##### 4.4.2 3D Simulations

##### 4.4.3 Human Connectome Project

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#### 4.7 Toolbox

### 5.1 Theory

#### 5.1.1 Transforming the Residual Field

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### 5.3 Results

#### 5.3.1 2D Simulations

#### 5.3.2 3D Simulations

#### 5.3.3 UK Biobank Data

#### 5.3.4 Comparison to Traditional Inference Procedures

### 5.4 Discussion

#### 5.4.1 Limitations

### 5.5 Conclusion

## CHAPTER 6

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### Conclusion and Future Work

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