Fixed versus random effects models for fMRI meta-analysis

Han Bossier¹
Ruth Seurinck¹
Beatrijs Moerkerke¹
Simone Kühn²

¹Department of Data Analysis, Faculty of Psychology and Educational Sciences, Ghent University, Belgium (EU)
²Max Planck Institute for Human Development, Berlin, Germany (EU)

August 12, 2015
Table of Contents

1 fMRI
2 Problem
3 Meta-analysis
4 of fMRI data
5 Validation
6 Study
7 Discussion
8 References
Brain: > 100,000 voxels: small artificial cubicles.

Multiple testing!

3 different pooling methods for 2nd level analysis (fixed effects, OLS and mixed effects).

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

FOR EACH VOXEL:
\[ Y_i = b_0 + b_1 X + \epsilon_i \]

SECOND LEVEL ANALYSIS WITH N=6

FOR EACH VOXEL:
\[ Y_i = b_0 + b_1 X + \epsilon_i \]
Results of group analysis.

Clusters of activity are summarized through local maxima

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Size (mm)</th>
<th>Voxels</th>
<th>Peak X</th>
<th>Peak Y</th>
<th>Peak Z</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57834</td>
<td>2142</td>
<td>12.0</td>
<td>41.0</td>
<td>13.0</td>
<td>13.88</td>
</tr>
<tr>
<td>2</td>
<td>30753</td>
<td>1139</td>
<td>25.0</td>
<td>18.0</td>
<td>13.0</td>
<td>12.27</td>
</tr>
<tr>
<td>3</td>
<td>25920</td>
<td>960</td>
<td>11.0</td>
<td>23.0</td>
<td>18.0</td>
<td>12.60</td>
</tr>
<tr>
<td>4</td>
<td>12690</td>
<td>470</td>
<td>43.0</td>
<td>38.0</td>
<td>12.0</td>
<td>9.57</td>
</tr>
<tr>
<td>5</td>
<td>11286</td>
<td>418</td>
<td>21.0</td>
<td>20.0</td>
<td>28.0</td>
<td>10.50</td>
</tr>
<tr>
<td>6</td>
<td>10125</td>
<td>375</td>
<td>18.0</td>
<td>22.0</td>
<td>9.0</td>
<td>12.58</td>
</tr>
<tr>
<td>7</td>
<td>10098</td>
<td>374</td>
<td>31.0</td>
<td>20.0</td>
<td>27.0</td>
<td>9.75</td>
</tr>
<tr>
<td>8</td>
<td>4293</td>
<td>159</td>
<td>8.0</td>
<td>45.0</td>
<td>31.0</td>
<td>8.94</td>
</tr>
</tbody>
</table>
Increasingly fMRI publications

Publications with keyword 'fMRI' in Web of Science.
However...

- fMRI studies tend to:
However...

- fMRI studies tend to:
  - have small sample sizes (< 30 subjects; David et al., 2013).
However...

- fMRI studies tend to:
  - have small sample sizes (< 30 subjects; David et al., 2013).
  - mainly control type I error rates while ignoring power issues (Durnez et al., 2014).
However...

- fMRI studies tend to:
  - have small sample sizes (< 30 subjects; David et al., 2013).
  - mainly control type I error rates while ignoring power issues (Durnez et al., 2014).
  - lack topological stability: variability of peak locations (in 3D space) over studies (Roels et al., 2015).
However...

- fMRI studies tend to:
  - have small sample sizes (< 30 subjects; David et al., 2013).
  - mainly control type I error rates while ignoring power issues (Durnez et al., 2014).
  - lack topological stability: variability of peak locations (in 3D space) over studies (Roels et al., 2015).

- Reproducibility is limited!
  ⇒ need to aggregate data over studies and over laboratories.
  ⇒ meta-analysis is a perfect tool to achieve this.
Meta-analysis

- Clinical trials.
- Summarize findings for increased power.
- Focus on effect sizes.
- Weighted average:
  - Within study variance
  - True effect size + between-study variance: yes (random) or no (fixed)?

Borenstein et al, 2009
Weighted average

\[ M = \frac{\sum_{i=1}^{k} W_i ES_i}{\sum_{i=1}^{k} W_i} \]

With \( M \) = weighted average, \( W_i \) the weight given to study \( i \) and \( ES_i \) its effect size.

**Fixed effects:**

\[ ES_i = \mu + \epsilon_i \]

Weights: within study variance only.

**Random effects:**

\[ ES_{ij} = \mu + \zeta_j + \epsilon_i \]

Weights: within and between study variance.
Meta-analysis of fMRI data

- Effect size (meta-analysis) in each voxel!
- Coordinate based meta-analysis:
  - Vote-counting (ALE, Eickhoff et al., 2009).
  - Transform t-values of peaks to effect sizes → weighted average.
    - Fixed effects meta-analysis.
    - Random effects meta-analysis (ES-SDM, Radua et al., 2012).
Existing methods

Fixed versus random effects models for fMRI meta-analysis
Inference: multiple testing

- Vote-counting procedure, ALE (probability of a peak at a particular voxel):
  - Uncorrected
  - False discovery rate (FDR), assuming independence or positive dependence in the data (Genovese et al., 2002).
  - FDR without any assumptions.

- Fixed and random effects meta-analyses (ES-SDM):
  - Whole brain permutations: shuffling locations of effect sizes around over studies.
  - Null distribution.
  - No correction for multiple testing!
Validating meta-analytical methods

- Reliability $\uparrow$ and reproducibility $\uparrow$: check performance of meta-analyses!
  - Type I error rate
  - Type II error rate
  - Topological stability

- We need extensive validation:
  - Within study-level parameters (e.g. sample size, pooling method of group analysis, etc...).
  - Between study parameters (e.g. different meta-analyses methods).
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
  - Mixed effects pooling: iteratively estimating between- and within-subjects variance separately.
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
  - Mixed effects pooling: iteratively estimating between- and within-subjects variance separately.
- Between-study parameters: three meta-analytical procedures
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
  - Mixed effects pooling: iteratively estimating between- and within-subjects variance separately.
- Between-study parameters: three meta-analytical procedures
  - Vote counting (ALE).
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
  - Mixed effects pooling: iteratively estimating between- and within-subjects variance separately.
- Between-study parameters: three meta-analytical procedures
  - Vote counting (ALE).
  - Fixed effects meta-analysis.
Addressing validation

- Use real data (IMAGEN project: 1400 subjects available).
- Within-study level parameters: three pooling methods for group analysis.
  - Fixed effects pooling: assumes no between-subjects variance.
  - Ordinary least squares: assumes homogeneous between-subjects variances.
  - Mixed effects pooling: iteratively estimating between- and within-subjects variance separately.
- Between-study parameters: three meta-analytical procedures
  - Vote counting (ALE).
  - Fixed effects meta-analysis.
  - Random effects meta-analysis (ES-SDM).
Design: resampling with respect to scanning site.

NUMBER OF ITERATIONS = 10

sample = 400
within site

$N_{TOT} = 1480$

$N_1 = 200$
$N_2 = 200$

$k = 10$

Fixed Effects

OLS

Mixed Effects

Fixed Effects

OLS

Mixed Effects

Fixed Meta-Analysis

Random Meta-Analysis (ES-SDM)

ALE

Ground Truth

FPR

Power

Overlap

Mixed Effects

FDR: $p < 0.001$
False positive rate, power and stability

- White square: Ground Truth
- Blob: meta-analysis
- Black: false positives (type I errors)
- Grey: lack of power (type II errors)
- Overlap: topological stability (Maitra, 2009).
Average Overlap

Pooling subjects:
- Fixed Effect
- OLS
- Mixed Effect

Meta-analysis method:
- Fixed Effects MA
- Random Effects MA
- ALE pID
- ALE pN
- ALE Uncorrected

Overlap

Fixed versus random effects models for fMRI meta-analysis
Fixed versus random effects models for fMRI meta-analysis

Average Power

Pooling subjects:
- Fixed Effect
- OLS
- Mixed Effect

Meta-analysis method:
- Fixed Effects MA
- Random Effects MA
- ALE pID
- ALE pN
- ALE Uncorrected

Power

Han Bossier
Department of Data Analysis
Average FPR

Pooling subjects:
- Fixed Effect
- OLS
- Mixed Effect

Meta-analysis method:
- Fixed Effects MA
- Random Effects MA
- ALE Uncorrected

Han Bossier
Fixed versus random effects models for fMRI meta-analysis
Summarizing

- Study level ⇒ meta-analysis: Mixed effects or OLS (!)
- Random and fixed effects meta-analyses outperform vote counting procedures.
- Random effects meta-analyses are to be preferred!
- Trade-off in size and amount of studies in the meta-analysis?
- Effect of thresholding at study-level?
Figures:
- J. Durnez

Data:
- Support was provided by the IMAGEN project, which receives research funding from the European Community’s Sixth Framework Programme (LSHM-CT-2007-037286).

Publications:
Gain from individual studies to meta-analysis (P < .05). Controlling for site = TRUE

- Overlap
- Power
- FPR

Pooling subjects

Gain from individual studies to meta-analysis (P < .05). Controlling for site = TRUE

Analysis:
- Studies
- Fixed Effects MA
- Random Effects MA
- ALEpID MA
- ALEpN MA
- ALE Uncorrected MA

Han Bossier
Fixed versus random effects models for fMRI meta-analysis
Remarks

- Trade-off in size and amount of studies in the meta-analysis?
- Effect of thresholding at study-level?
- Future:
  - Effect of missing data in coordinate based meta-analysis (due to using only peak locations).
  - Effect of violations of assumptions such as normality of effect sizes.
  - Other between-study variance estimators?