

Detecting and Interpreting Heterogeneity and Publication Bias in Image-Based Meta-Analyses

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Introduction

With the increase of data sharing, meta-analyses are becoming increasingly important in the neuroimaging community. They provide a quantitative summary of published results and heightened confidence due to higher statistical power. The gold standard approach to combine results from neuroimaging studies is an Image-Based Meta-Analysis (IBMA) [1] in which group-level maps from different studies are combined.

Recently, we have introduced the IBMA toolbox, an extension for SPM that provides methods for combining image maps from multiple studies [2]. However, until recently the toolbox lacked diagnostic tools used to assess critical assumptions of meta-analysis, in particular whether there is inter-study variation requiring random-effects IBMA, and whether publication bias is present. Here, we present two new tools added to the IBMA toolbox to detect heterogeneity and to assess evidence of publication bias.

Methods: Heterogeneity

- The term ‘Study Heterogeneity’ refers to the systematic variation in summary statistics between studies.
- The degree of heterogeneity present can affect many design choices during meta-analysis (e.g. whether to do RFX or FFX analysis for example).

- Heterogeneity can be tested for in the IBMA toolbox using Cochran’s Q statistic [3]:

$$Q := \sum_{i=1}^n w_i (\hat{\theta}_i - \hat{\theta})^2$$

Where $\hat{\theta}_i$ is the observed effect at a voxel in study i , $\hat{\theta}$ is the average of $\hat{\theta}_i$ across all studies at said voxel and w_i is the inverse variance of the $\hat{\theta}_i$.

- To test the Heterogeneity toolbox options, 21 fMRI studies investigating pain stimuli were used. From this selection the average Z map and the Q statistic map were generated for comparison.

Methods: Publication Bias

- The term ‘Publication Bias’ refers to the tendency of published literature to overestimate statistical parameters.
- For a given voxel, in the IBMA toolbox, plots can be generated to detect publication bias:
 - A Funnel Plot shows study effect size against standard error
 - A Gailbraith plot shows study inverse standard error against standardized effect size.
- Several publication bias measures have been implemented in the IBMA toolbox. These are:

Name	Brief Description
Egger’s Regression [4]	Regression is performed on a Galbraith plot to test whether the intercept passes through the origin.
Macaskill’s Regression [4]	Regression is performed on a funnel plot to test whether the slope is negative.
Trim And Fill [5]	A ranking system is used to estimate the number of studies missing due to publication bias.
Begg’s Correlation [6]	A correlation test is performed on a funnel plot to test for a negative correlation.

- To test these, we simulated 200 ‘studies’ with smooth zero-mean 3D Gaussian fields of size $50 \times 50 \times 50$ representing standardized signal and smooth 3D χ^2 fields representing variance. Following this, an arbitrary $4 \times 4 \times 4$ cube-shaped region was selected.

- The 50 ‘studies’ with the highest mean value in the cube-shaped region were selected and constituted a ‘biased’ selection, where the bias would be expected in the cube of interest.

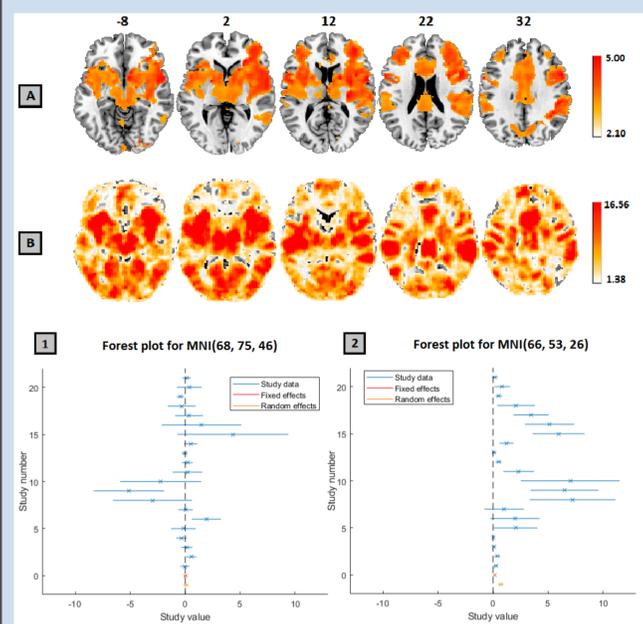
Results

On the 21 fMRI studies, the Q-Statistic found evidence for heterogeneity at nearly every voxel in the brain (Fig 1). This finding is likely due to the different stimuli and designs used in each study.

On simulated data, the publication bias test statistics successfully identified the region in which bias was induced (Fig 2). It can be seen that publication bias was detected in the region bias was induced at (highlighted in yellow in Fig 2A).

The induced bias can also be visually deduced from the voxelwise funnel plots produced. For example, the even scatter in Fig 2.2 implies no evidence of publication bias, whilst the uneven scatter in Fig 2.1 implies strong evidence of publication bias.

Figure 1



The thresholded Z map, from a meta-analysis of the 21 pain studies (A) and the Q-statistic P-Value map thresholded at a corresponding FDR value of 0.05 (B). Forest plots for two voxels, one with no significant observed signal (1) and one with significant observed signal (2). P-values are displayed with a $-\log_{10}$ scale.

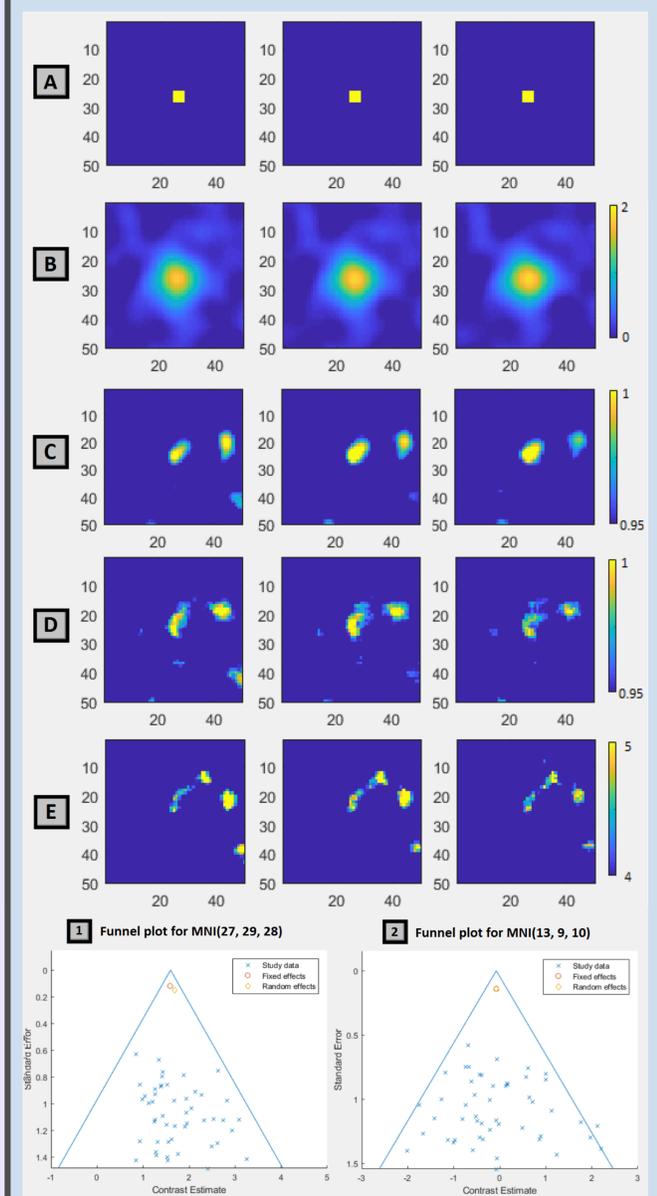
Conclusion

The Publication Bias and Heterogeneity detection measures, alongside the IBMA toolbox itself, allow input of NIDM packs [7] or NIfTI images and are open-source and freely available extensions of SPM. They can be found at:

<https://github.com/NeuroimagingMetaAnalysis/ibma>

These tools form an important first step towards making efficient, statistically valid synthesis of neuroimaging literature easily accessible to the research community.

Figure 2



The region in which publication bias was induced (highlighted in yellow) (A). The average Z map across the biased selection (B). The region detected as biased by Begg’s correlation (C). The region detected as biased by Egger’s regression (Unweighted) (D). The region detected as biased by Trim and Fill (E). Funnel plots for two voxels, one with significant observed publication bias (1) and one with no significant observed publication bias (2).

Acknowledgements

This work was supported by the Wellcome Trust. We gratefully acknowledge the use of the pain dataset from the Tracey pain group, FMRI, Oxford. The majority of this work was conducted while TMS, TEN and CM were at the University of Warwick.

References

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