Assessing publication bias in coordinate-based meta-analysis techniques

Freya Acar[1], Ruth Seurinck[1], Simone Kühn[2], Beatrijs Moerkerke[1]
[1] Ghent University, Department of Data Analysis, [2] Max Planck Institute for Human Development, Berlin
Ghent University

Meta-analysis of functional Magnetic Resonance Imaging (fMRI)

Coordinate-based meta-analysis is a popular method for fMRI, these toolboxes have been developed:

- Activation Likelihood Estimation (ALE) [2,3]
- Multi-level Kernel Density Analysis (MKDA)[4]
- Seed-based d Mapping [5] (uses peak height as effect size when available)

Meta-analyses require publication bias diagnostics

- Publication bias: studies that fail to show significance in a certain region fail to get published
- This study introduces publication bias measures for coordinate-based meta-analysis methods that do not rely on effect sizes (e.g. ALE)

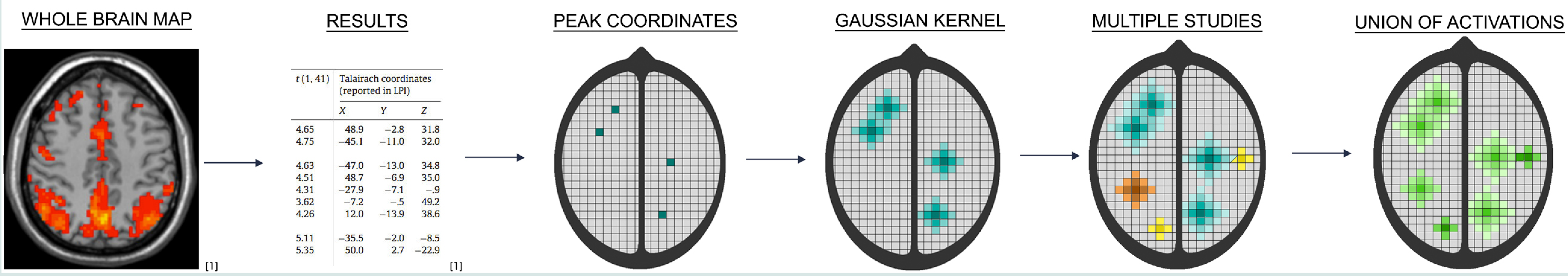


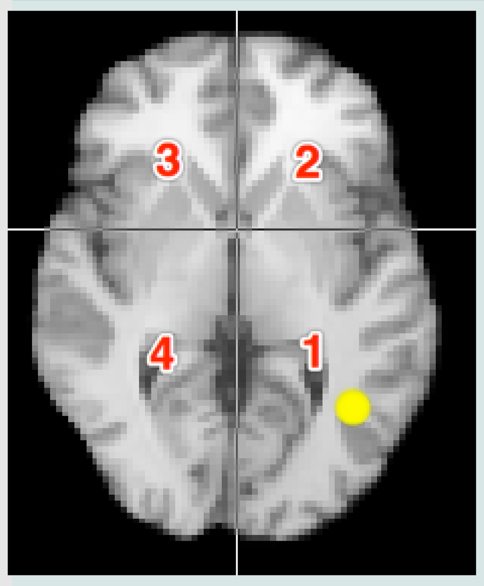
Figure 1: Overview of ALE meta-analysis.

Introduction of 2 methods for the assessment of publication bias:

① Fail-Safe N[6] (test for % contributing studies)

How many null studies can be added to a meta-analysis showing a significant effect in a region before the result is no longer statistically significant?

Simulation study



- 3 'real' studies with 1 peak in target region distance on average 3mm from location true activation
- Null studies each 1 peak in quadrant 2,3 or 4
- Effect of sample size: small (n∼10), medium (n∼20) or large (n∼30), se=1
- Effect of thresholding: 7 thresholding methods

Figure 2: The brain is divided in 4 quadrants for simulations, true activation at the location of the yellow dot.

Results and discussion

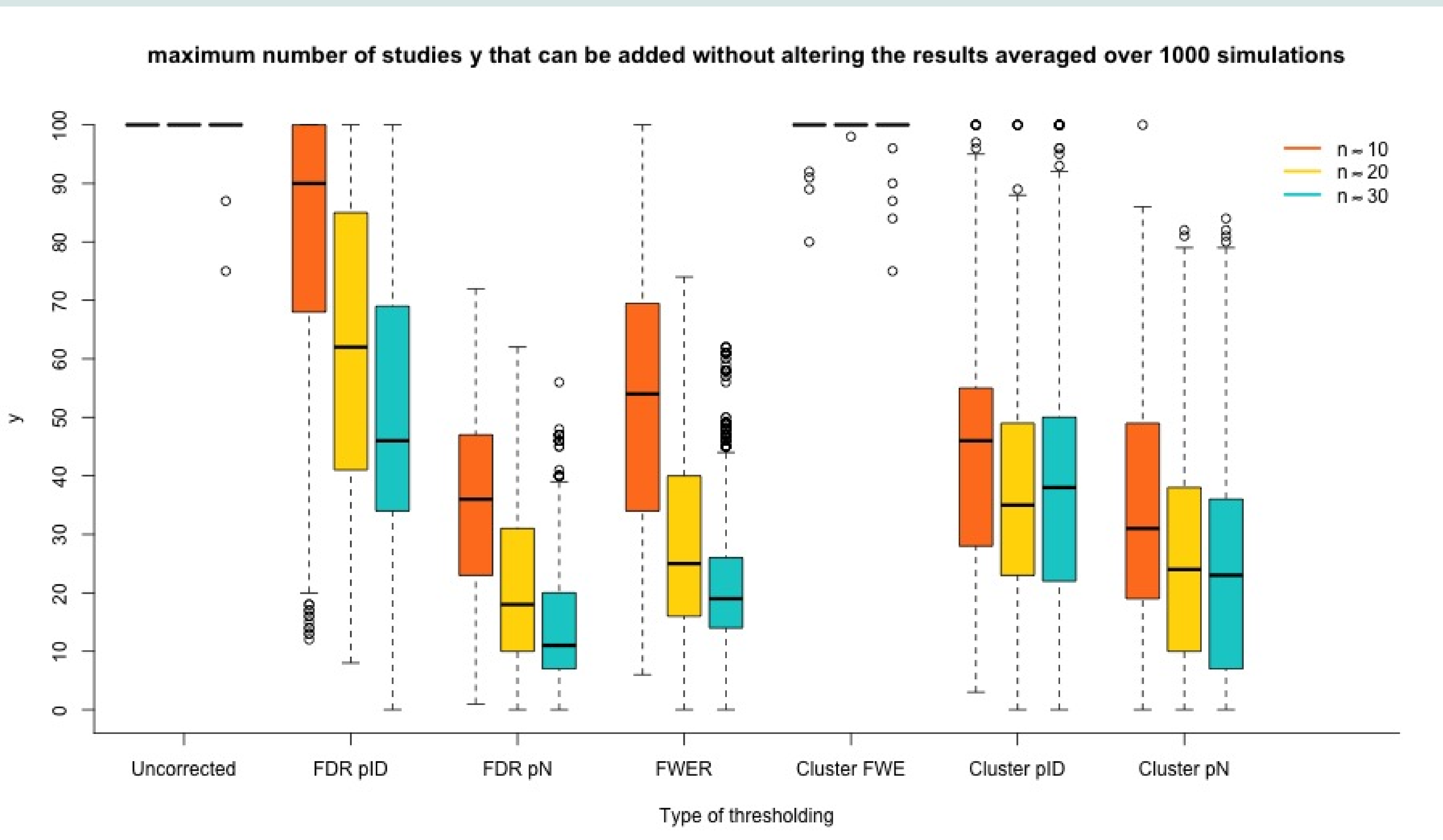


Figure 3: Amount of null studies that can be added to a meta-analysis of 3 studies before the target cluster is no longer statistically significant, by thresholding method and average sample size.

Robustness versus leniency:

- Big influence of both thresholding method and sample size
- A lot of variability within conditions
- What is an acceptable number of null studies that can be added without altering the results?
  - Too low? Points at non-robust results. (In spirit of classic Fail-Safe N [5])
  - Too high? One or a small number of studies drives the entire analysis
  - Results for sample size: contra-intuitive for robustness but intuitive for leniency
- Uncorrected thresholding shows large influence of small number of studies [9]

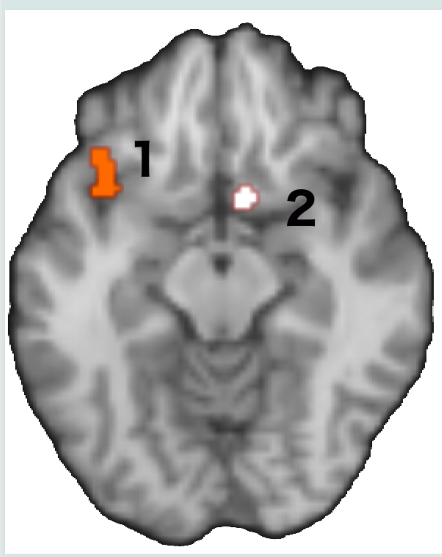
② Regression test for sample size of contributing studies [8]

Verifies whether the resulting clusters of a meta-analysis are caused by activation foci stemming from small studies (small sample bias).

How does it work?

- Sleuth database was searched for experiments with paradigm class 'taste'.
- Contrast taste > no taste was selected (87 studies, 529 foci).
- Voxel FWE < 0.05 thresholding resulted in 4 statistically significant clusters.
- Two of these clusters are plotted below and checked for a small sample bias.

This meta-analysis is conducted solely for demonstration, references on request.



Study	n	Contribution to cluster?	
		1	2
1	12	Yes	No
2	8	Yes	No
3	11	No	Yes
4	6	Yes	Yes
5	15	No	Yes
6	14	No	Yes
...	...	...	...

Given a significant ALE cluster,

- included studies get a value of 0 (did not contribute to cluster) or 1 (contributed to cluster)
- activation (x-axis) is plotted against sample size (y-axis)
- slope gives an indication about publication bias

Figure 4: Two significant clusters and a selection of studies, their sample sizes and whether they have foci that contributed to the clusters.

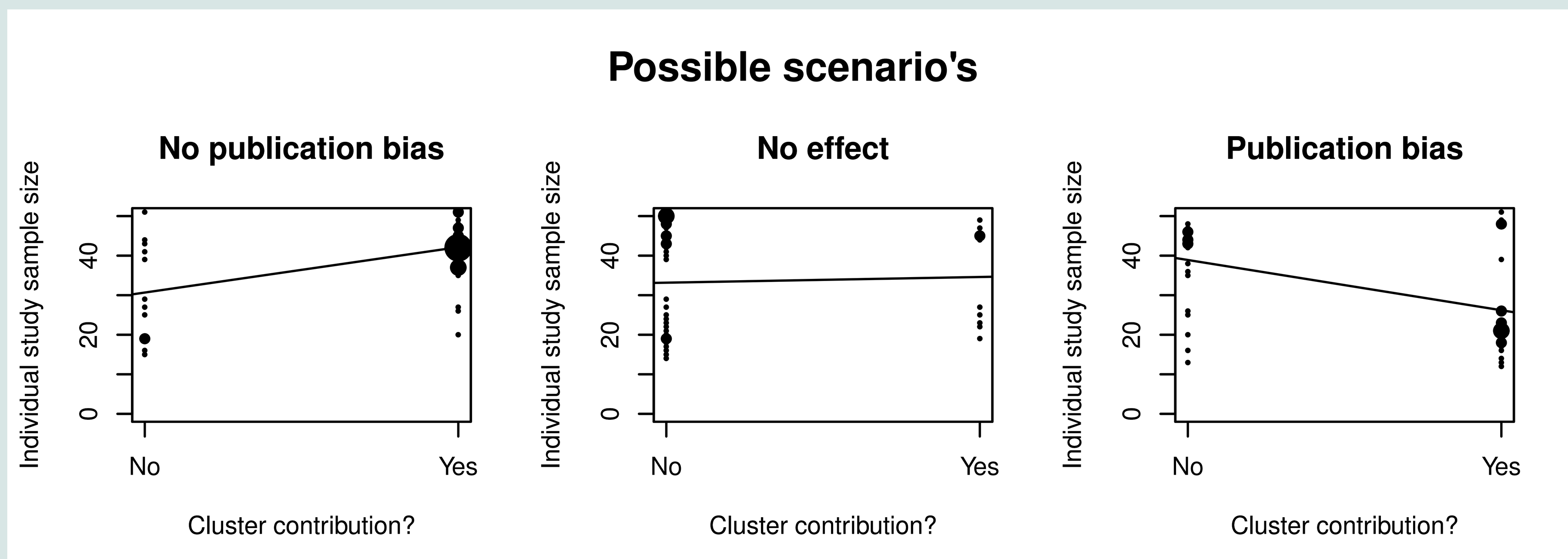


Figure 5: Possible patterns based on presence or absence of publication bias.

Results and discussion

- Results indicate a small sample bias for the first cluster, not for the second.
- Effect of thresholding at study level?

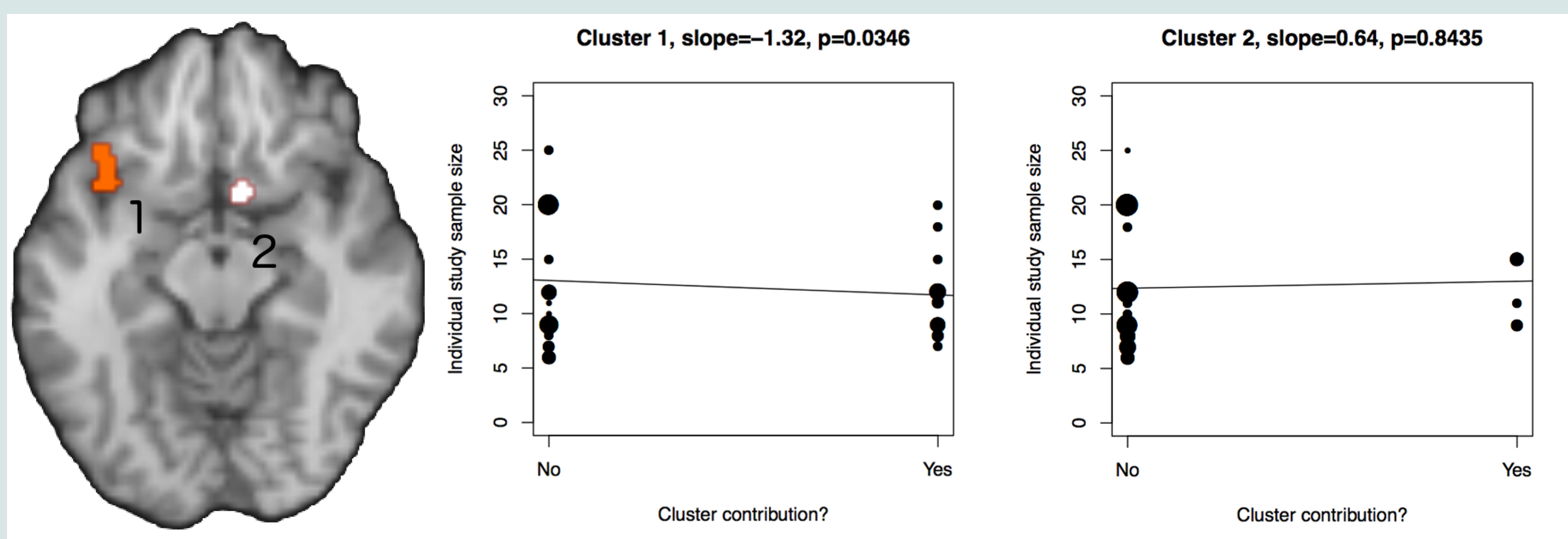


Figure 6: Regression test results for each of the two depicted clusters.

[1] Han et al. (2015) *Progress in Neuro-Psychopharm. & Biol. Psychiatry*, 59.
[2] Eickhoff et al., (2009, 2012). *Human Brain Mapping*, 30; *Neuroimage*, 59.
[3] Turkeltaub et al., (2012). *Human Brain Mapping*, 33.
[4] Wager et al., (2009). *Neuroimage*, 45.
[5] Radua et al., (2009, 2010, 2012, 2014). *Br J Psychiatry*, 195; *Arch Gen Psychiatry*, 67; *Eur Psychiatry*, 59; *Front Psychiatry*, 59.
[6] Rosenthal, (1979). *Human Brain Mapping*, 33.
[7] Light & Pillimer, (1984).
[8] Egger & Smith, (1997). *BMJ*, 315.
[9] Eickhoff et al., (2016). *Neuroimage*, 173.