Meta-analyses of fMRI studies

Beatrijs Moerkerke

Department of Data-analysis, Ghent University

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200 JAAR
UNIVERSITEIT GENT

FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES

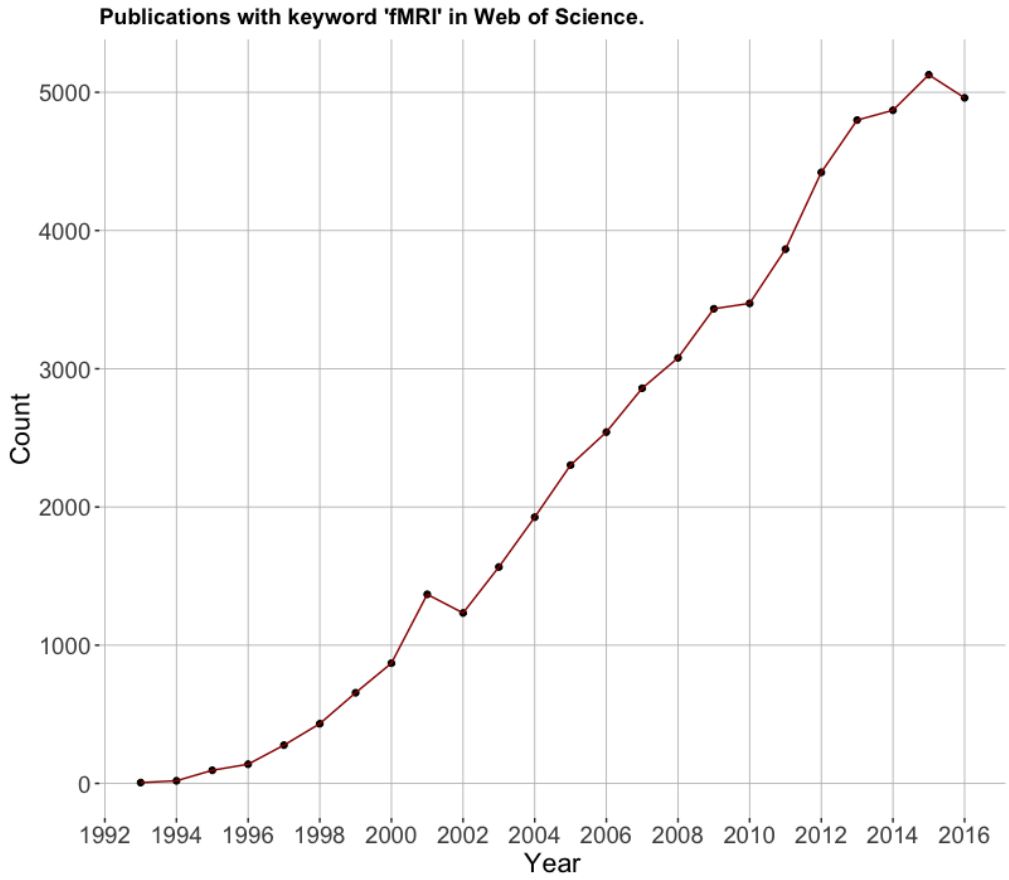
fwo Research Foundation Flanders
Opening new horizons

Why meta-analytic approach?

- fMRI studies tend to
  - have small sample sizes (Poldrack et al., 2017)
  - focus on type I error rate control while ignoring power issues (Durnez et al., 2014)
  - lack topological stability of peak locations (Roels et al., 2015)
- Reproducibility is limited

Why meta-analytic approach?

- Yearly $>$ 5 000 publications using fMRI
- Re-use existing research
- Aggregate data over over studies and labs



Overview

1. Classical meta-analyses and meta-analyses for fMRI studies
2. What information is available at study-level?
3. Image-based meta-analyses
4. Coordinate-based meta-analyses
5. Publication bias
6. Discussion

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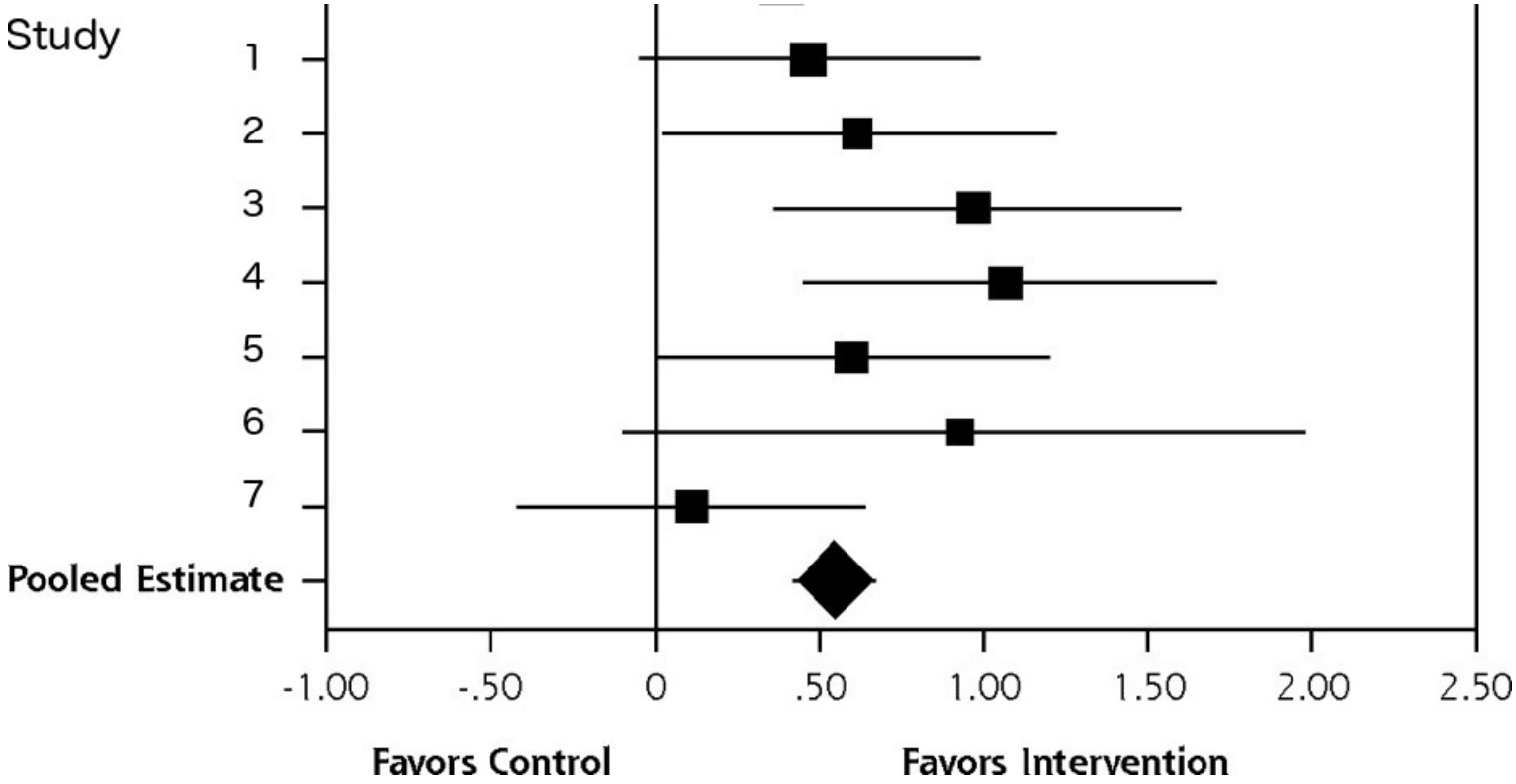
Classical meta-analyses

What is the general goal of a meta-analysis?

Estimate the overall underlying true effect size of an experimental manipulation or association across studies and assess the variation in effect size as a function of study characteristics.

Classical meta-analyses

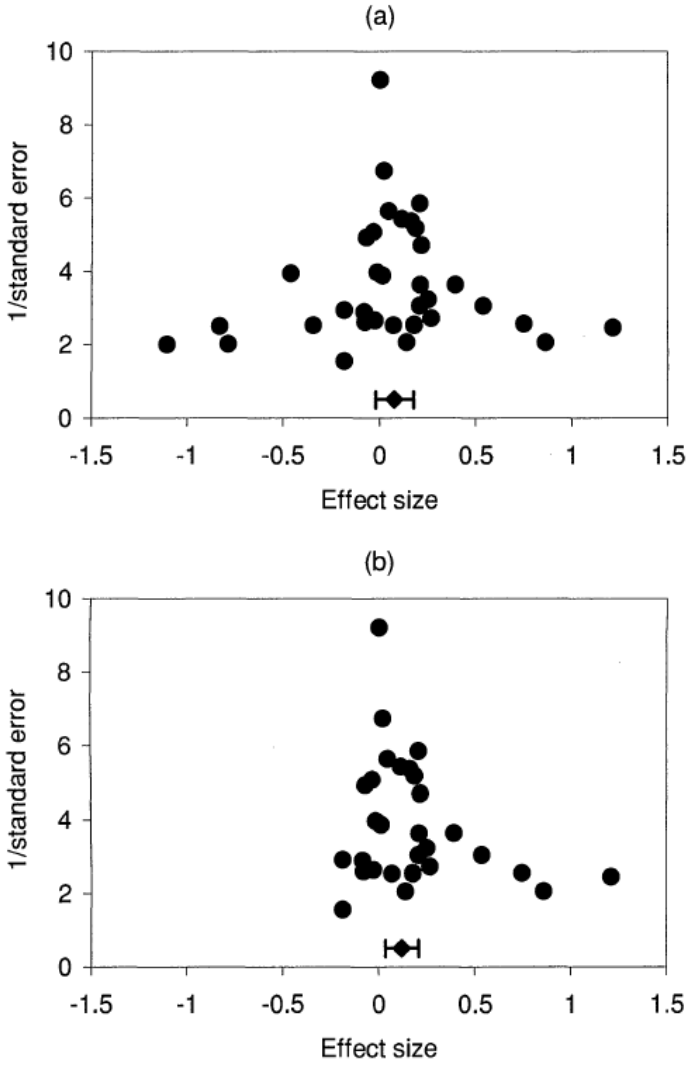


Modified from Baskerville, Liddy, & Hogg (2012)

Classical meta-analyses

Publication bias - *File drawer problem*

Classical meta-analyses



Duval and Tweedie (2000)

(a) no publication bias

(b) publication bias

Classical meta-analyses

Essential ingredients:

- Selection of studies
- Effect size + variation per study (no p-values!)
- Combination of study results
  - *Overall effect size*
  - *Can study characteristics explain heterogeneity between studies?*
- Measures for publication bias
  - *Correction for publication bias*
  - *Sensitivity analyses*

Classical meta-analyses

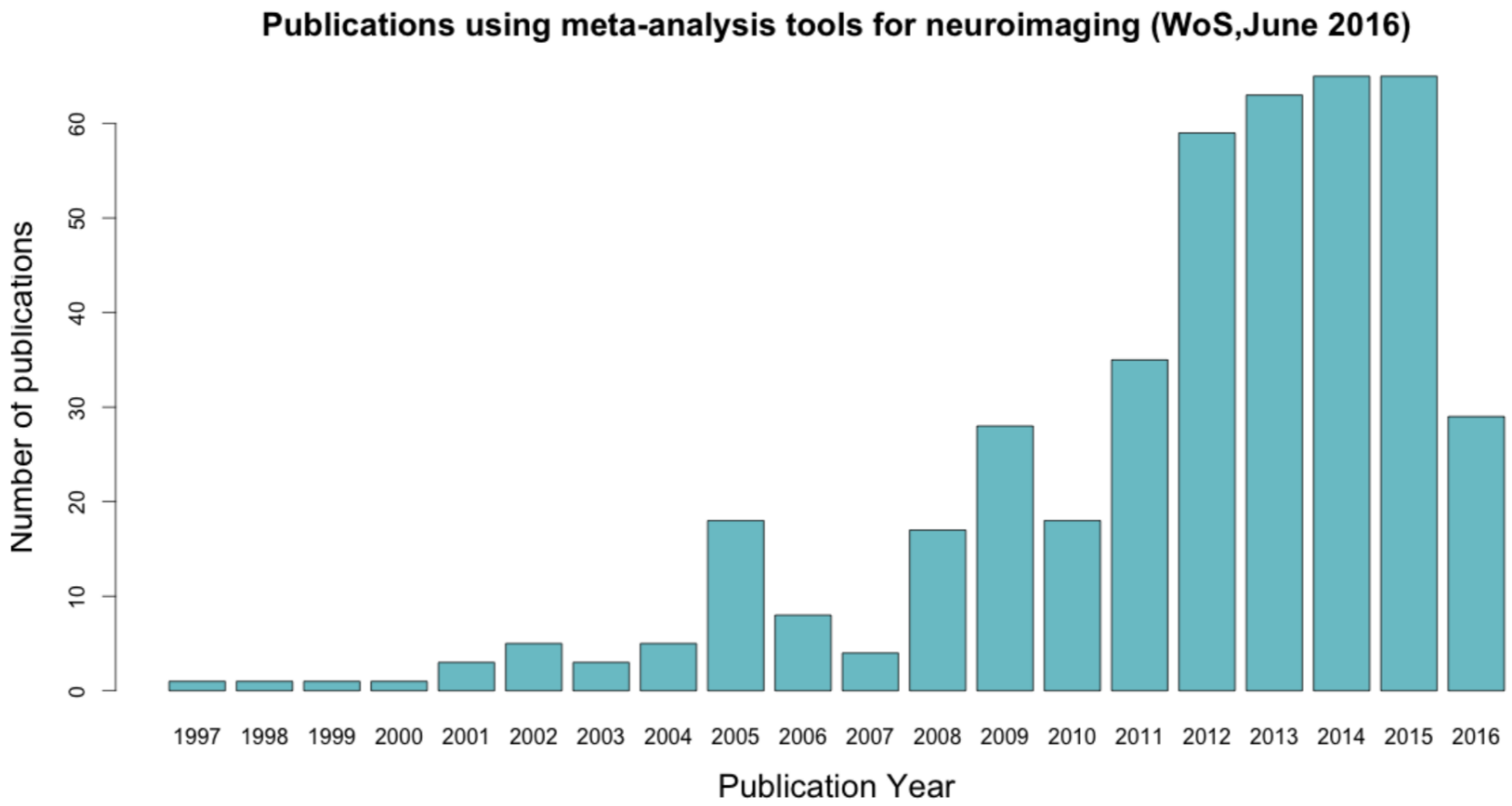
Meta-analysis: promising approach (also for neuroimaging)

Excellent method to aggegrate findings over studies and labs:

- increases power
- reduces type I errors
- identifies reproducible findings
- elucidates large variability in published results

$\Rightarrow$ Development and validation of techniques for meta-analysis in fMRI research.

Meta-analyses for neuroimaging



Meta-analyses for neuroimaging

High impact reviews on a variety of topics

NeuroImage

Volume 16, Issue 2, June 2002, Pages 331–348

View Menu

Review

Functional Neuroanatomy of Emotion: A Meta-Analysis of Emotion Activation Studies in PET and fMRI ☆

K.Luan Phan[a, 2], Tor Wager[b], Stephan F. Taylor[a], Israel Liberzon[a, c]

Meta-analyses for neuroimaging

Remember the 'essential ingredients' for a meta-analysis!

- Effect Sizes
  - $\Leftrightarrow$ statistical significance
  - independent of sample size
  - APA: report effect size with confidence interval
  - in fMRI? Voxelwise? Region/clusterwise? What if we only have peak information?

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Level of measurements for meta-analysis input

How to aggregate over studies?

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  Level of measurements for meta-analysis input

  How to aggregate over studies?
- Is there a problem with the selection of the input?

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  Publication Bias

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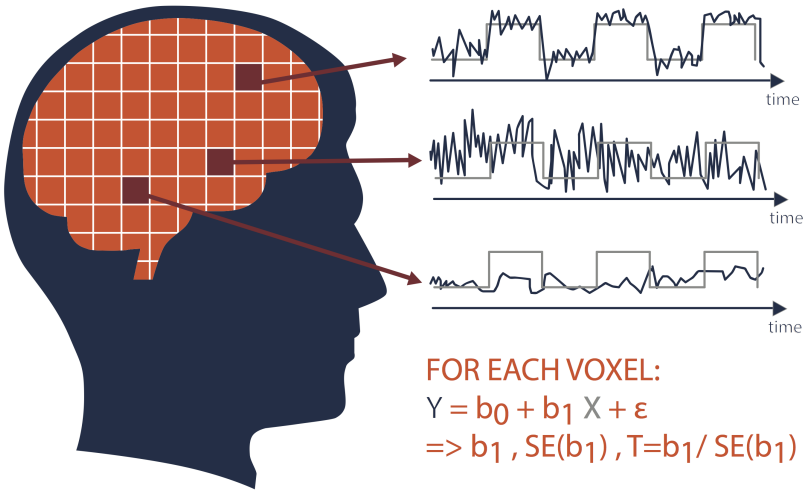
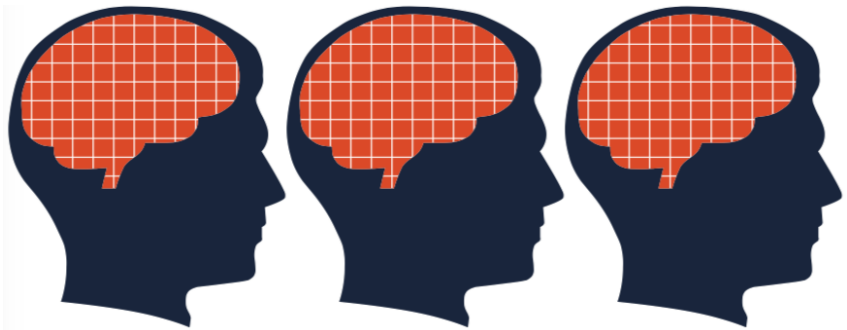
Available study-level information

Ideally . . .





OpenfMRI

Stanford Center for Reproducible Neuroscience

Russell Poldrack, Chris Gorgolewski

`https://openfmri.org`

Brain **I**maging **D**ata **S**tructure

Available study-level information

Reality . . .

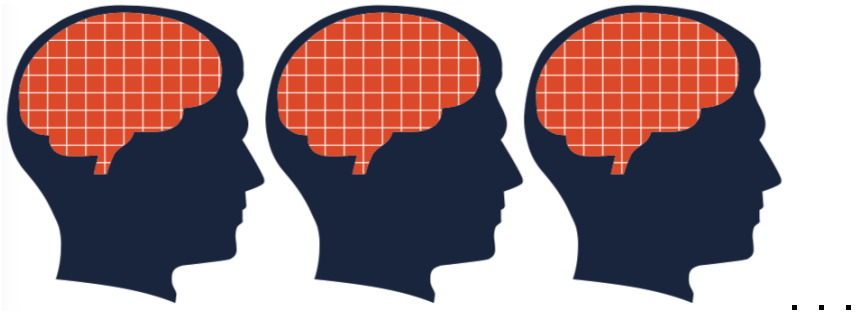
Anatomical Region	*Cluster Size*	*Hemisphere*	*Z Score*	*Stereotaxic Coordinates*		
Temporo-occipital fissure (hV5/MT+)	10	L	5.33	−40	−78	0
Temporo-occipital fissure (hV5/MT+)	63	L	5.32	−48	−72	−6
Transverse occipital sulcus	31	L	5.02	−26	−94	12
Posterior segment IPS (pIPS)	49	L	5.59	−24	−78	36
Posterior segment IPS (pIPS)	2	L	5.09	−20	−76	46
Posterior segment IPS (pIPS)	3	R	5.05	24	−72	48
Precuneus	288	L	6.21	−16	−64	52
Precuneus	230	R	5.87	16	−66	50
Middle segment IPS (mIPS)	247	L	5.83	−30	−54	62
Middle segment IPS (mIPS)	230	R	5.31	28	−56	54
Anterior segment IPS (aIPS)	247	L	5.31	−40	−38	46
Anterior segment IPS (aIPS)	52	R	5.44	34	−40	46
Superior frontal sulcus (dorsolateral premotor cortex)	240	L	6.02	−24	−4	58
Superior frontal sulcus (dorsolateral premotor cortex)	61	R	5.86	30	−6	56
Inferior frontal gyrus	7	R	5.16	40	6	34
Anterior cingulate sulcus	29	L	5.51	−10	20	42

Seurinck et al. (2011)

brainmap.org

Available study-level information

- Image or Intensity Based Meta-analysis (IBMA)



- Coordinate Based Meta-analysis (CBMA)

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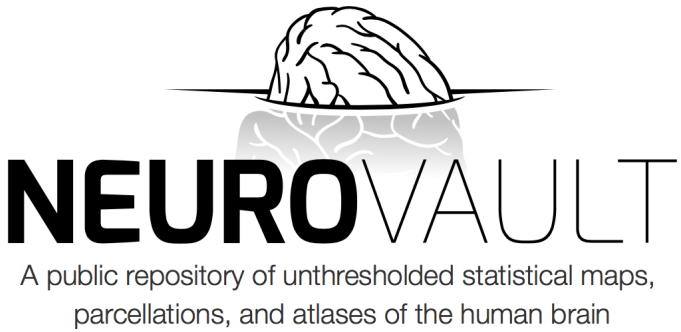
Image-based meta-analyses

- Full maps available: possible to add 'study' as a third level in a mixed effects GLM analysis.
- Minimum information required: contrast estimates for each voxel in each study with standard errors
- Alternatively: use fixed effects approach

Image-based meta-analyses

- IBMA also possible with less information available
  - Only statistics images - Z-based IBMA



Stanford Center for Reproducible Neuroscience
Russell Poldrack, Chris Gorgolewski

`https://neurovault.org`

  - Only contrast images available - GLM approach

- Toolbox for IBMA (SPM extension) - Camille Maumet, available on Github

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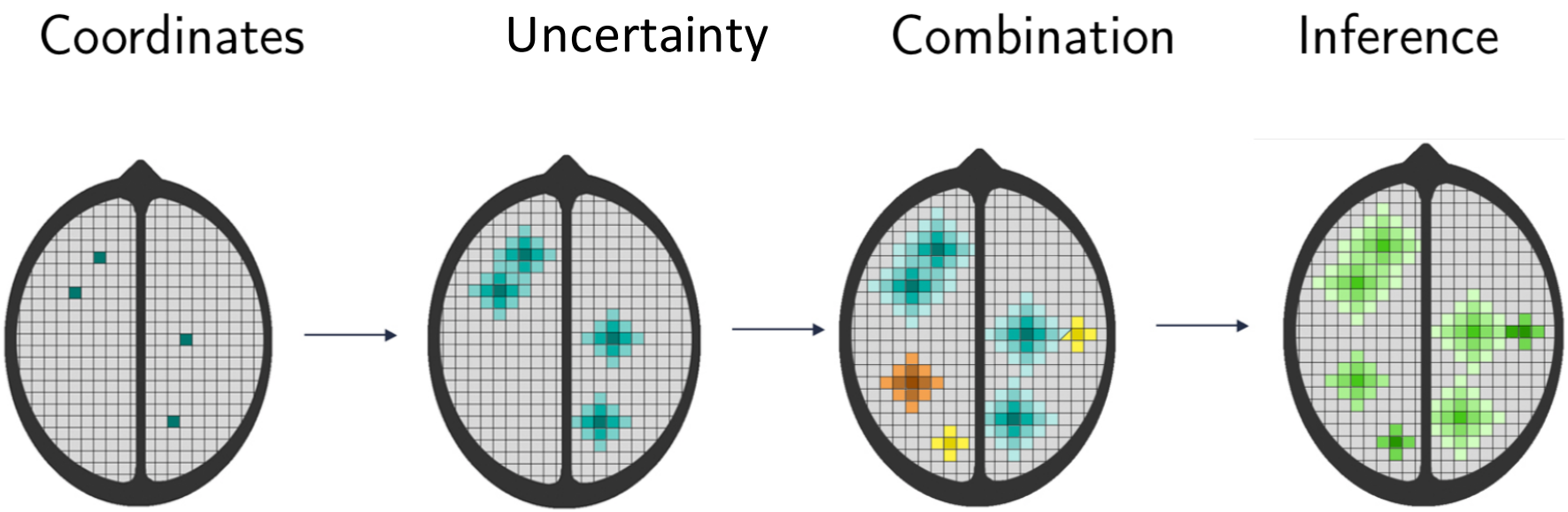
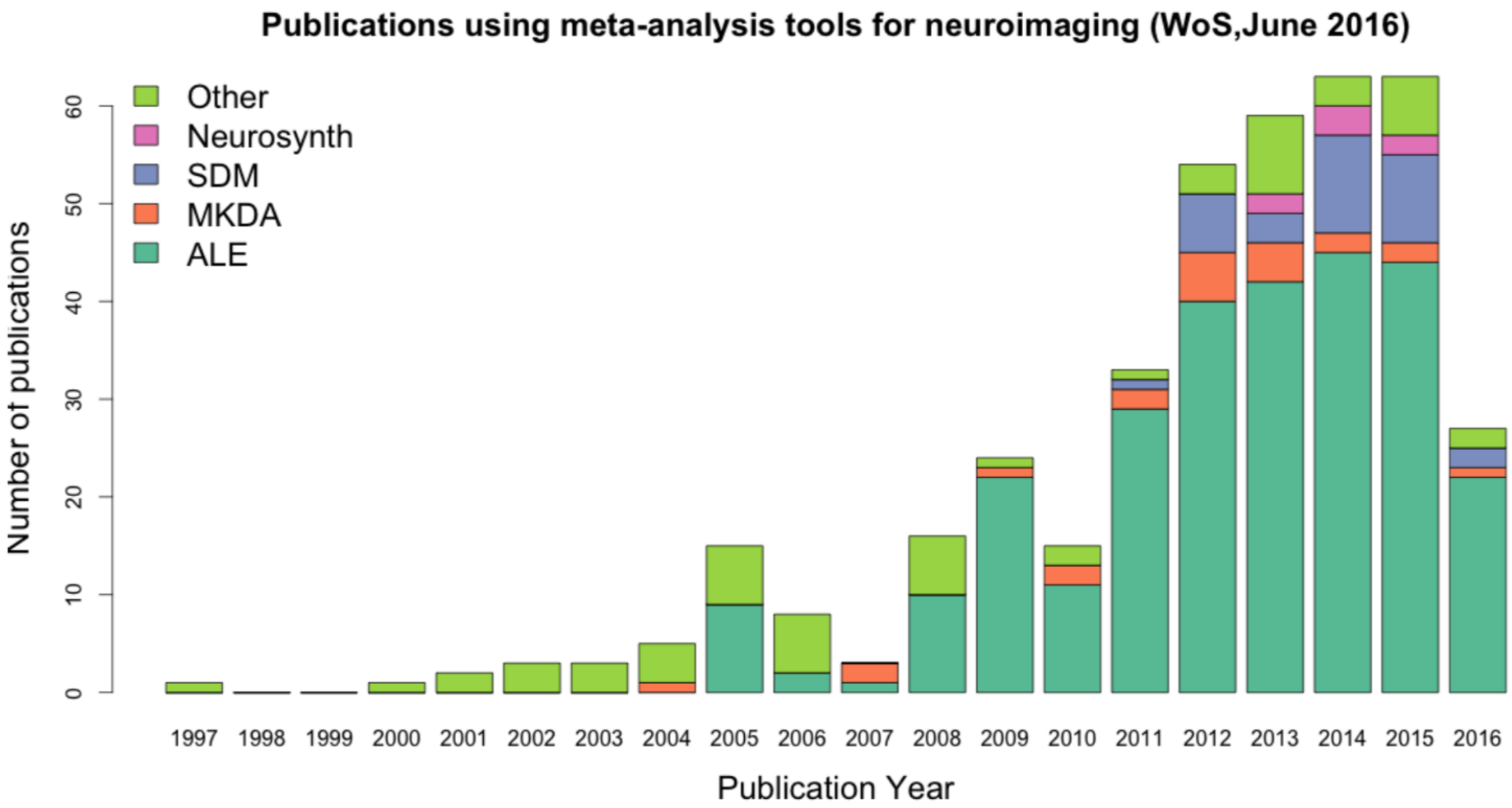
Coordinate-based meta-analyses



Coordinate-based meta-analyses

ALE	Activation Likelihood Estimation
	(Turkeltaub et al., 2002; Eickhoff et al. 2009)
MKDA	Multi Kernel Density Analysis
	(Wager et al., 2007; 2009)
SDM	Seed-based d Mapping
	(Radua et al., 2009, 2010, 2012, 2014)
Neurosynth.org	Platform for automatic large-scale meta-analysis
	(Yarkoni et al., 2011)

Coordinate-based meta-analyses



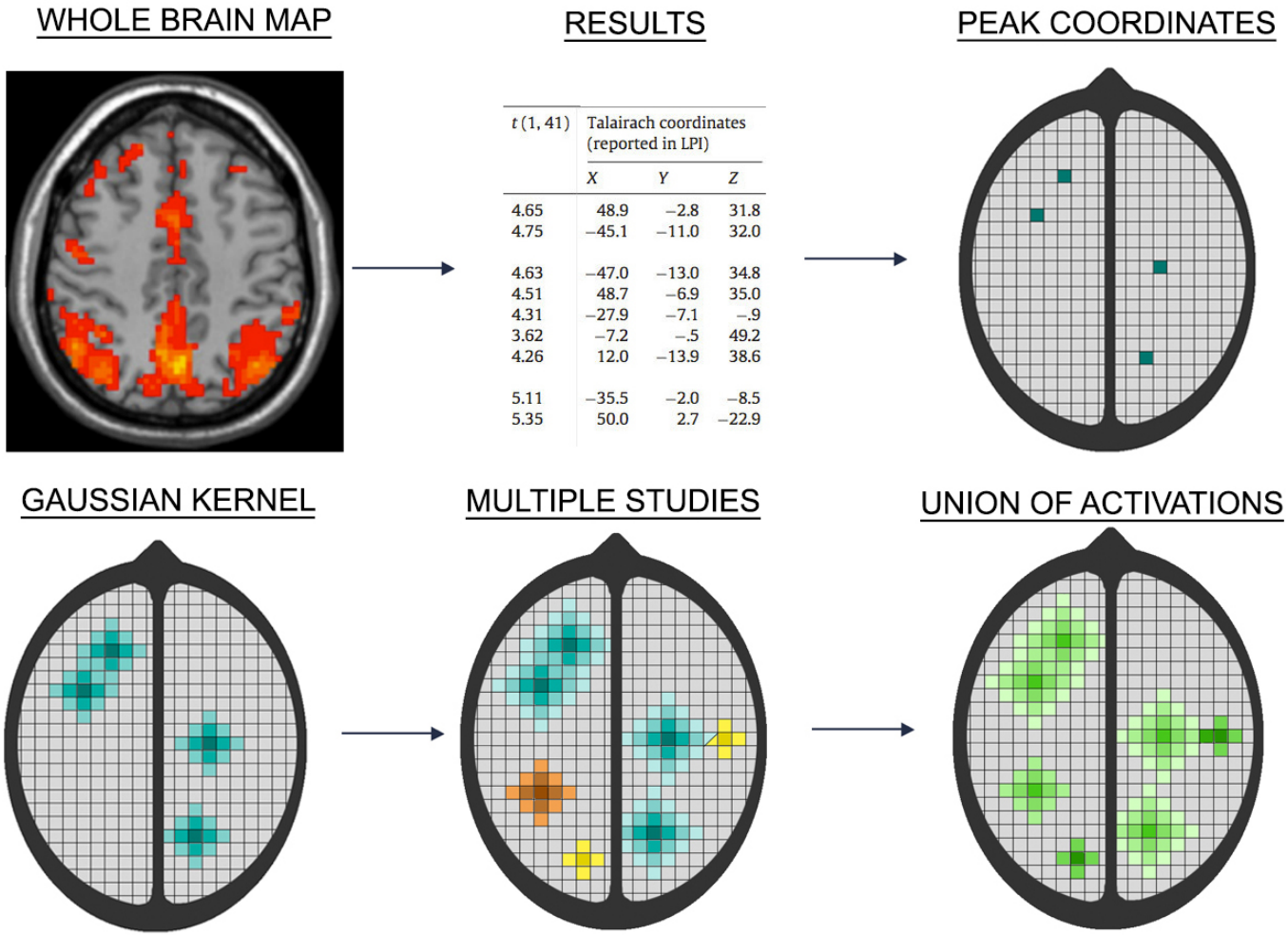
Coordinate-based meta-analyses

Activation Likelihood Estimation (ALE) algorithm

- User friendly
- Linked to large database of fMRI studies
- Based on spatial location, does not use effect sizes

Coordinate-based meta-analyses

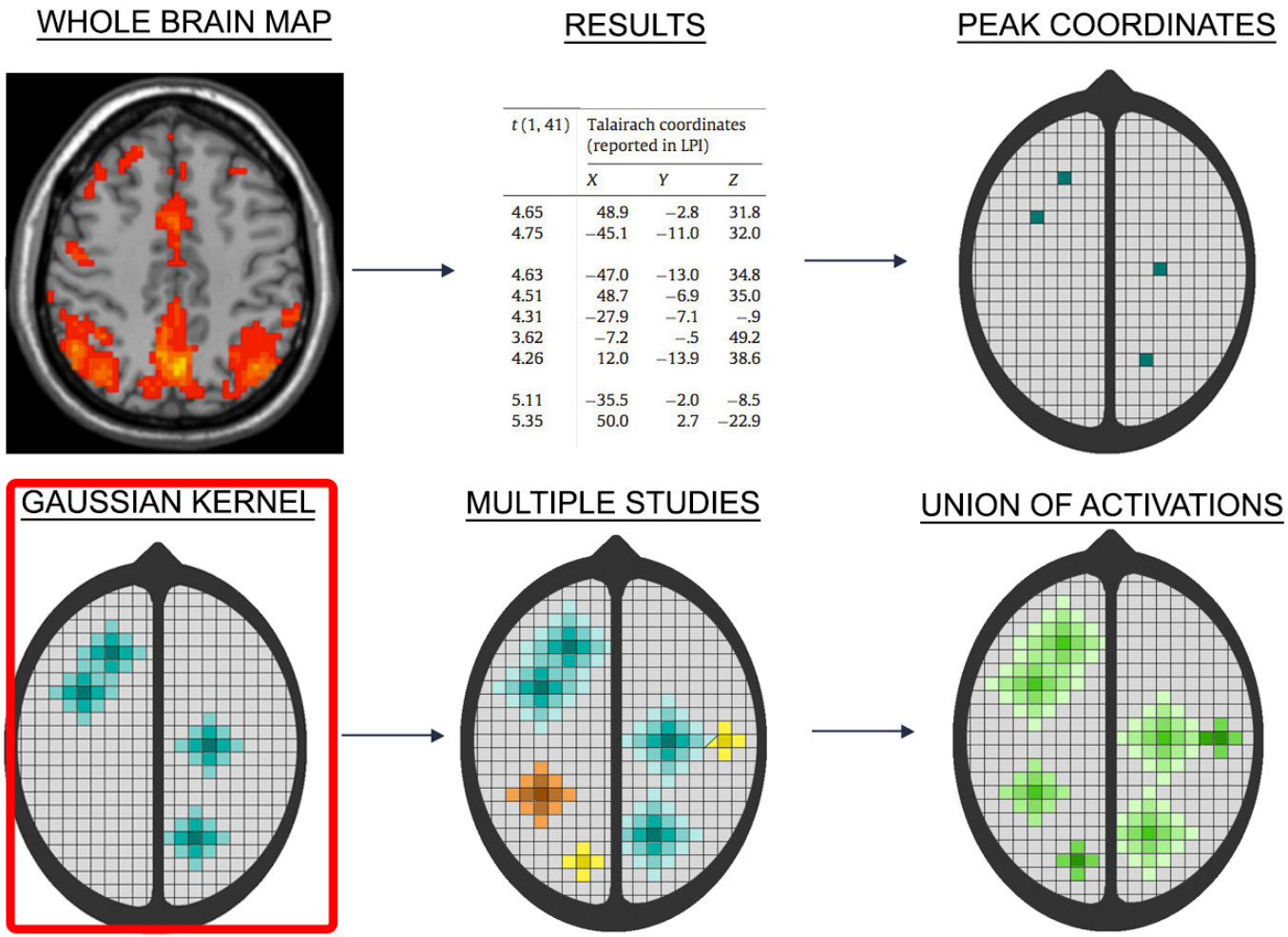
ALE algorithm



$t(1, 41)$	Talairach coordinates (reported in LPI)		
	X	*Y*	*Z*
4.65	48.9	−2.8	31.8
4.75	−45.1	−11.0	32.0
4.63	−47.0	−13.0	34.8
4.51	48.7	−6.9	35.0
4.31	−27.9	−7.1	−.9
3.62	−7.2	−.5	49.2
4.26	12.0	−13.9	38.6
5.11	−35.5	−2.0	−8.5
5.35	50.0	2.7	−22.9

Coordinate-based meta-analyses

ALE algorithm



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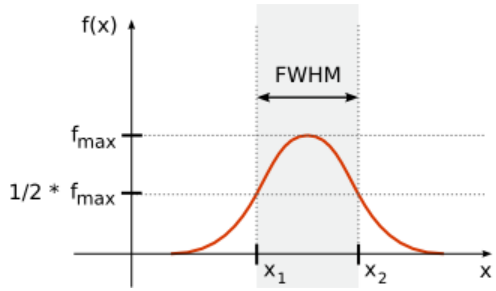
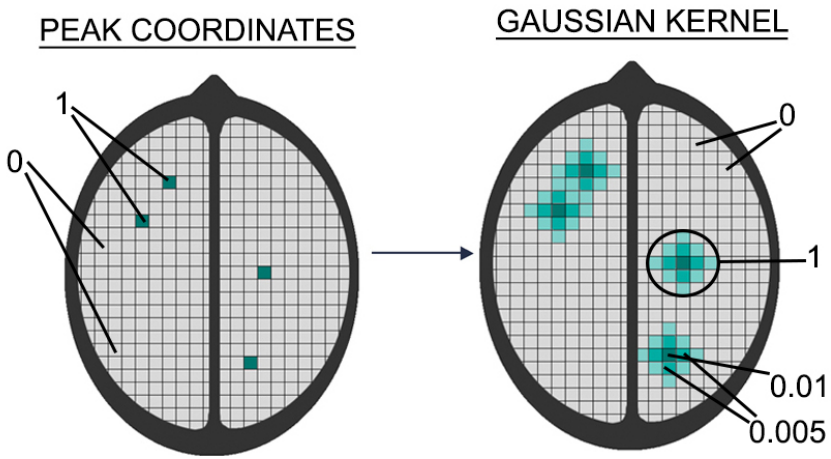
5.11	−35.5	−2.0	−8.5
5.35	50.0	2.7	−22.9

ALE: Gaussian kernel - **Uncertainty**

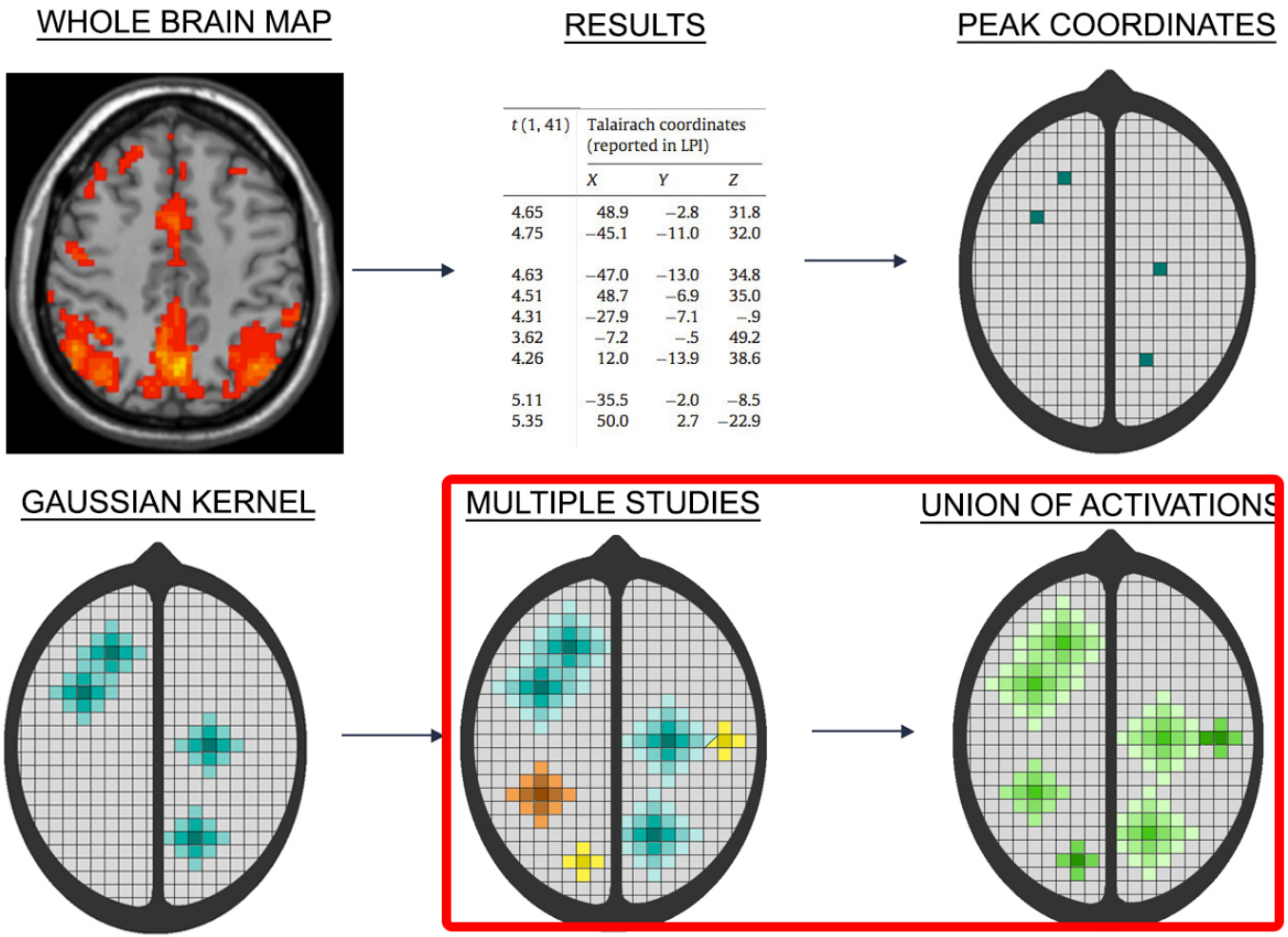
- Kernel smoothing captures spatial character of true activation
- Result: maps with modeled activation (MA-maps)
  - MA-value: for each voxel the probability of an activation being located at exactly that voxel.
  - Takes into account location and spatial uncertainty of reported coordinates of that study.
  - n ↑, spatial uncertainty ↓, FWHM ↓





Coordinate-based meta-analyses

ALE algorithm



ALE algorithm - **Combination**

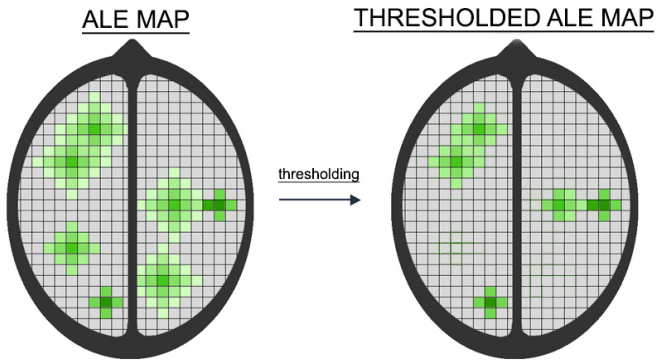
- In the individual studies (MA maps), all voxels i (i=1,...,V) have a value between 0 and 1.
- A union of these MA-values is computed to construct the summary ALE map.
- Suppose we have K studies (k=1,..,K), the ALE value in voxel i is equal to

$$ALE_i = 1 - \prod_{k=1}^{K}(1 - MA_{i,k})$$

ALE: Thresholding - **Inference**

- The statistical significance of the ALE value of each voxel needs to be determined
- Permutation procedure / analytical procedure
- Peak or cluster inference - corrections for multiple testing

ALE: Interpretation results - **Inference**



Interpretation statistical significance ALE value?

A widely used technique for coordinate-based meta-analysis of neuroimaging data is activation likelihood estimation (ALE), which determines the **convergence of foci** *reported from different experiments.*
Eickhoff et al. (2009)

Probability of observing one or more foci at a given location

Coordinate-based meta-analyses

Seed-based *d* Mapping

formerly "*Signed Differential Mapping*"

SDM

- Uses peak height (z-value)!
- Procedure that allows to combine complete test images and images with only peak information

Extra	Combination of full images with coordinates
Uncertainty	Kernel is weighted by the effect size (Hedges'g)
Combination	Voxelwise, classical random effects meta-analysis
Inference	Thresholding: permutation procedure no multiple comparisons procedure (missing data: effect size = 0)

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Validation of methods

- Simulations
- Sub-sampling from large-scale databases with single-subject fMRI data available

IMAGEN project
- $n \pm 2000$ (adolescents)
- on request

Human Connectome Project
- $n \pm 1200$
- freely available

UK Biobank
- $n \pm 500000$
- fee required

- Bossier et al. (2017): influence of group-level analysis on coordinate-based meta-analysis

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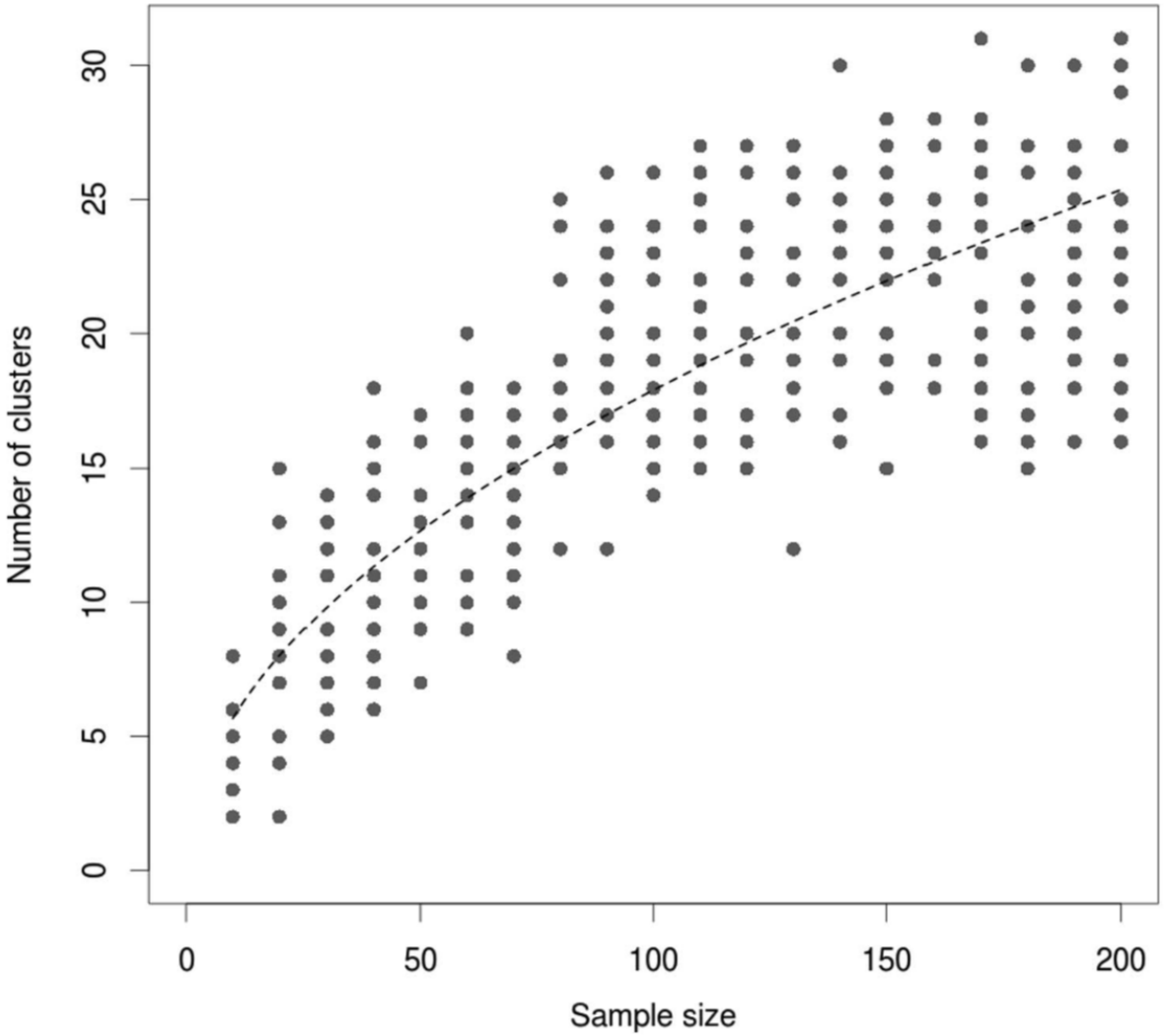
Publication bias

Publication bias occurs when the results of published and unpublished studies differ systematically.

(e.g. published studies show a statistically significant effect whereas unpublished studies do not show this effect)

Publication bias

Is there problem with publication bias in neuroimaging?



David et al. (2013)

Publication bias

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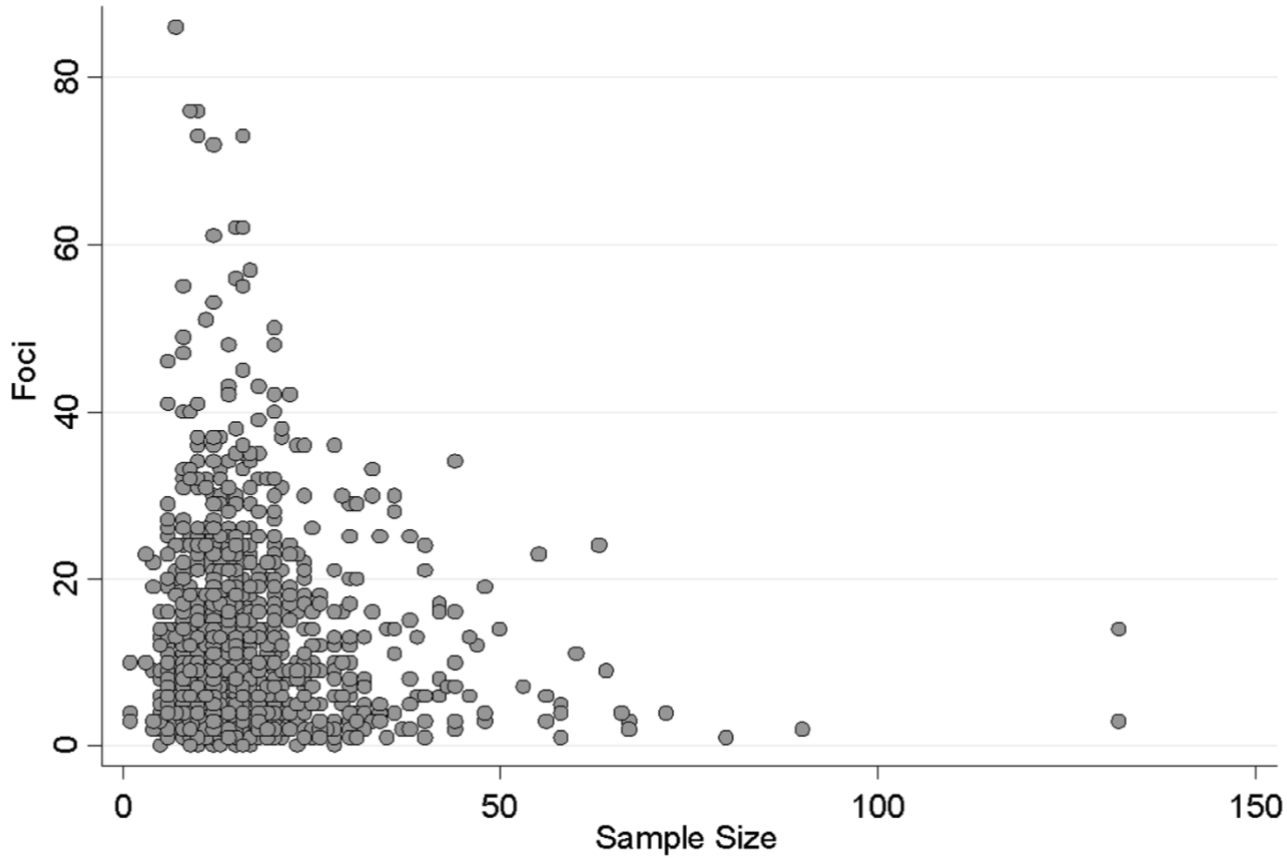


David et al. (2013)

Publication bias

Possible sources of publication bias:

- File drawer
- Censored reporting: missing information within studies
- Use of thresholded results: different thresholds over studies?
  e.g. small sample bias

Publication bias

How big is the fMRI file drawer?

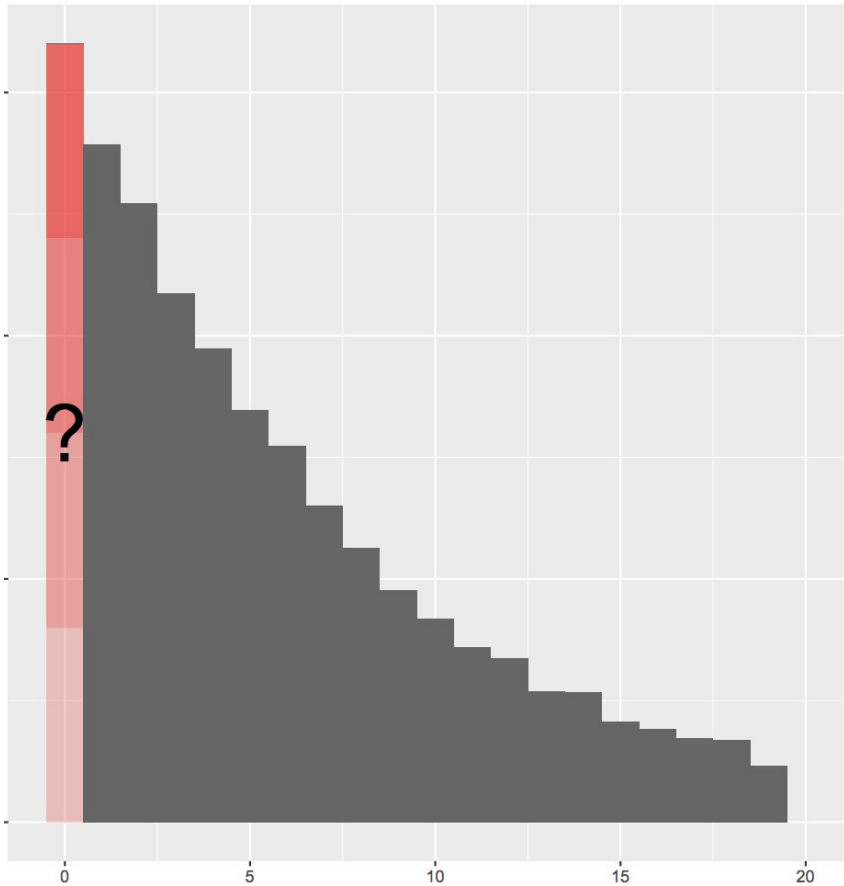
Samartsidis et al. (2017):

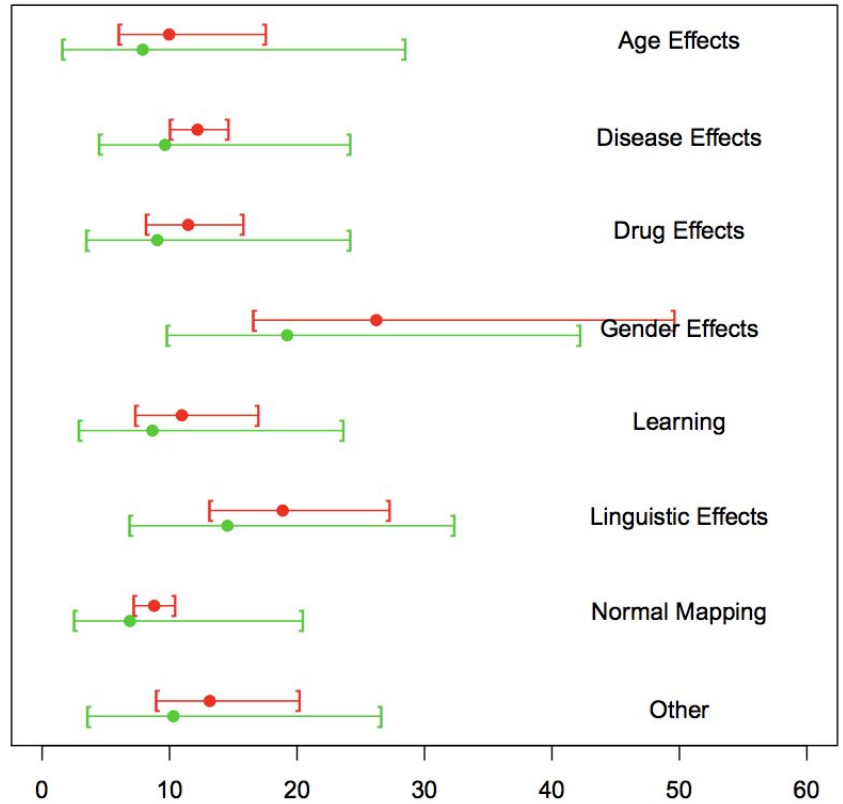
- Quantify file drawer problem in CBMA
- BrainMap database: use zero-truncated modeling approach to estimate prevalence of non-significant contrasts
- At least 6/100

Publication bias

How big is the fMRI file drawer?

Samartsidis et al. (2017):

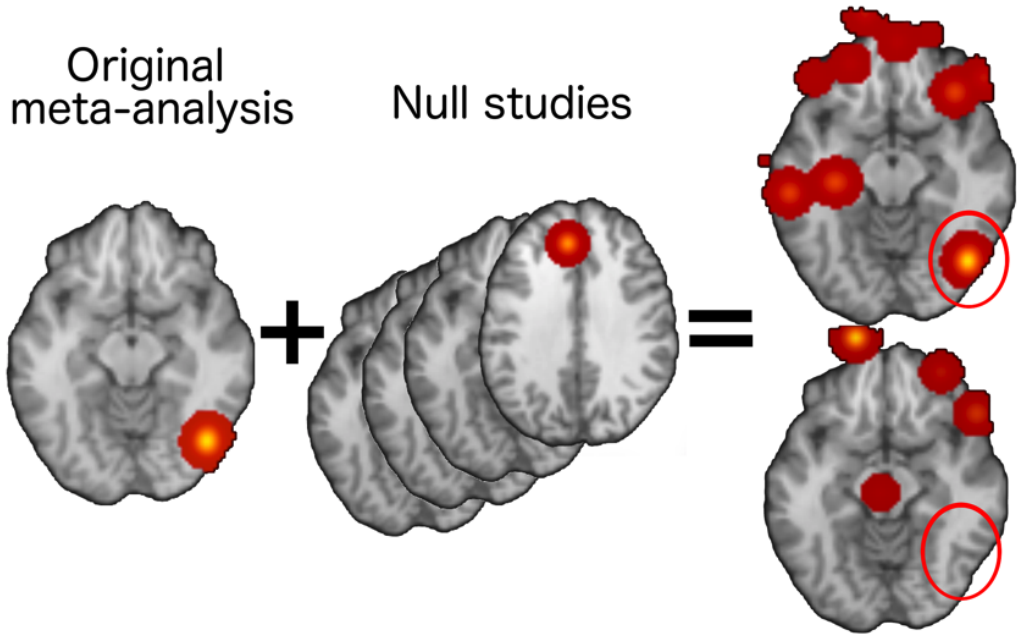




Publication bias

Acar et al. (2017):

Use fail-safe N (FSN) measure to quantify robustness of results against the possibility of file drawer problem



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?

Publication bias

ALE meta-analysis on finger tapping paradigm - 38 papers with $k = 73$

Cluster number	Volume (mm^3)	Weighted Center (x,y,z)			Extrema Value	Number of contributing studies	FSN
1	27736	-43.4	-21.8	48.1	0.105	59	> 730
2	14792	5.1	-56	-22.3	0.079	45	> 730
3	13704	39.5	-28.2	49.9	0.046	42	260
4	13640	-2.4	-2.7	53.1	0.092	53	> 730
5	11256	-24.9	-7.9	4.7	0.049	29	409
6	3504	20.3	-10.5	7.5	0.029	13	< 156
7	1968	55.7	6	16.8	0.022	10	< 24

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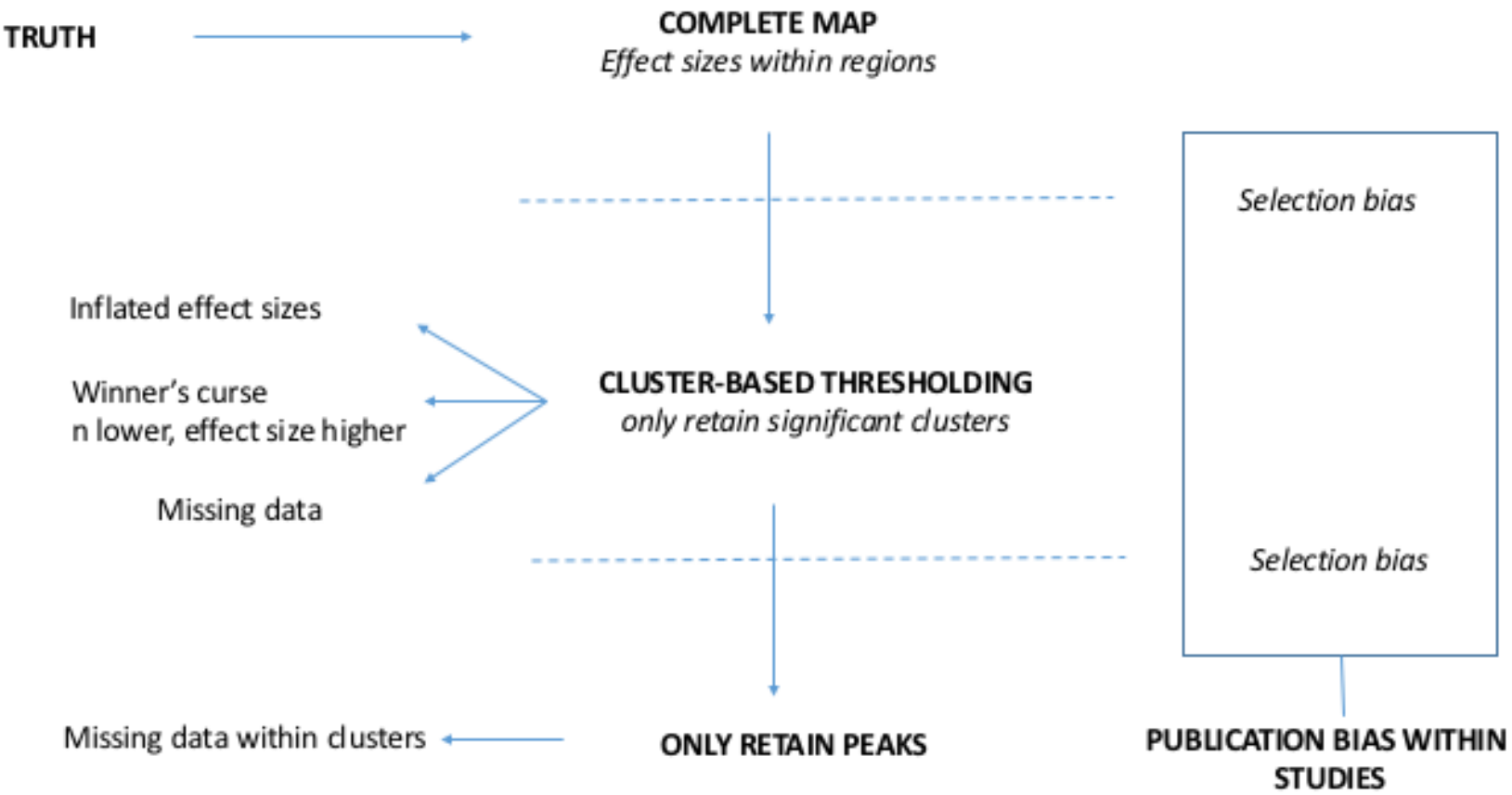
Publication bias



Publication bias

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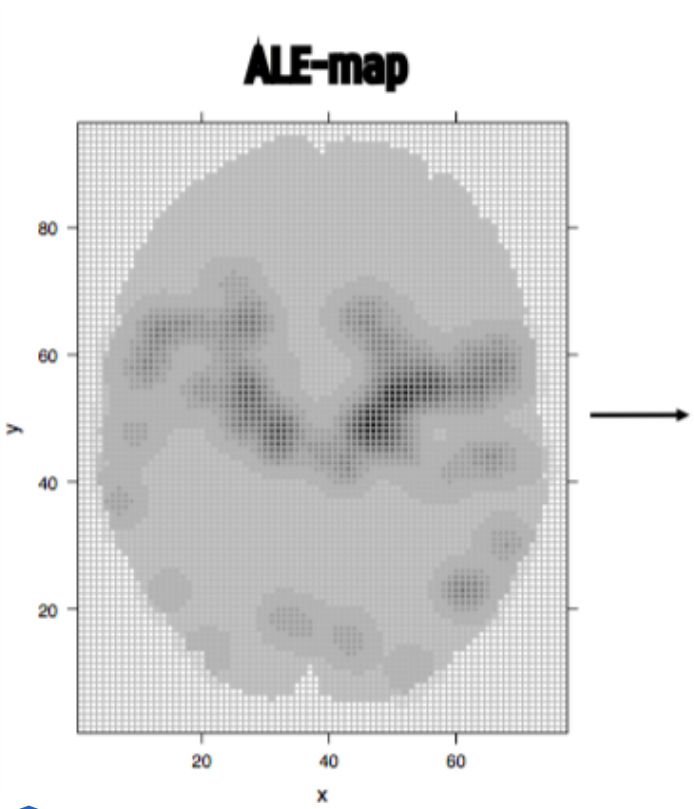
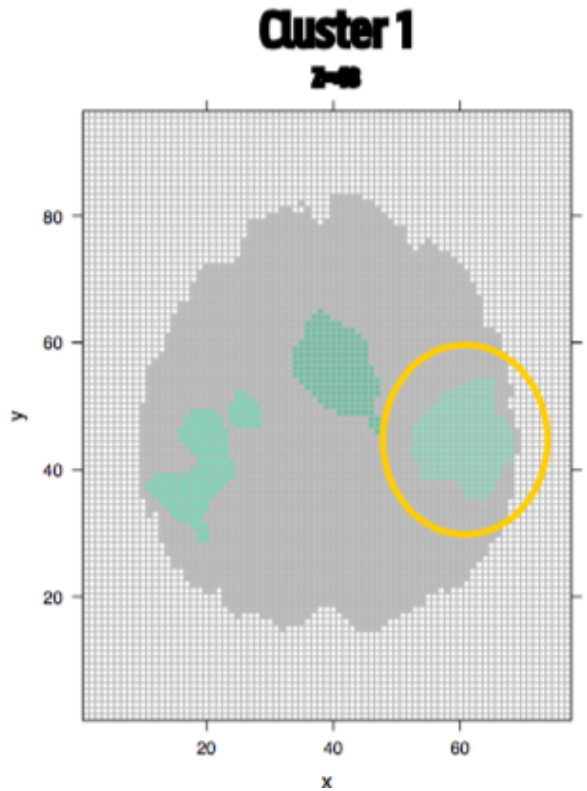
Publication bias

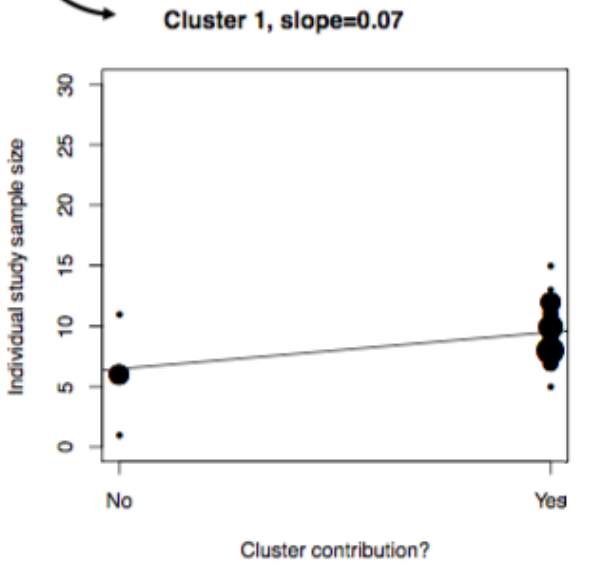
Acar et al. (in preparation): small sample bias

Example: ALE meta-analysis on the finger tapping paradigm





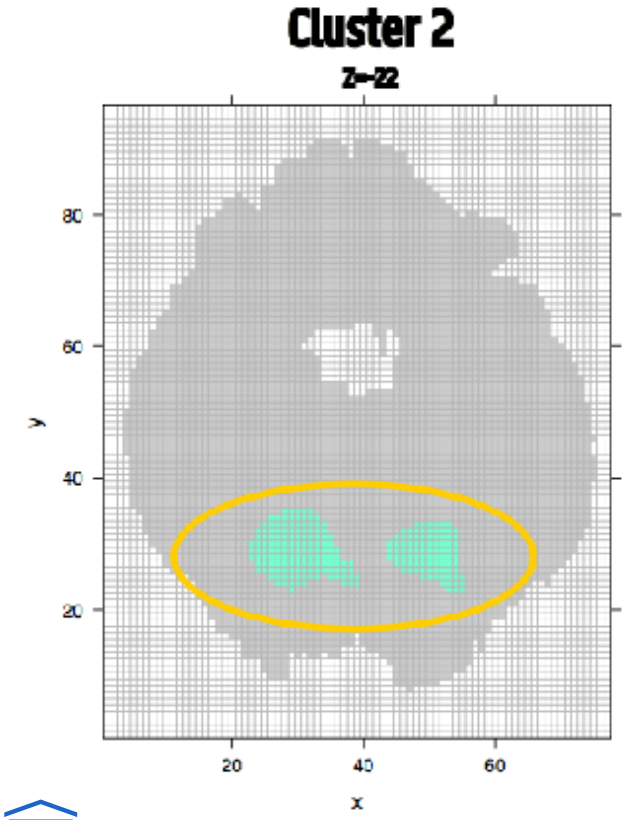
Study nr	1	2	3	...	73
Sample size	10	15	7	...	5
Contribution?	Yes	No	Yes	...	No



Publication bias

Acar et al. (in preparation): small sample bias

Example: ALE meta-analysis on the finger tapping paradigm



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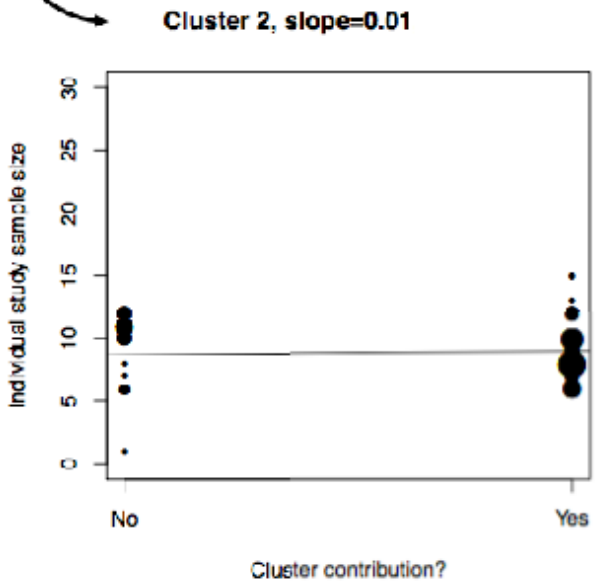
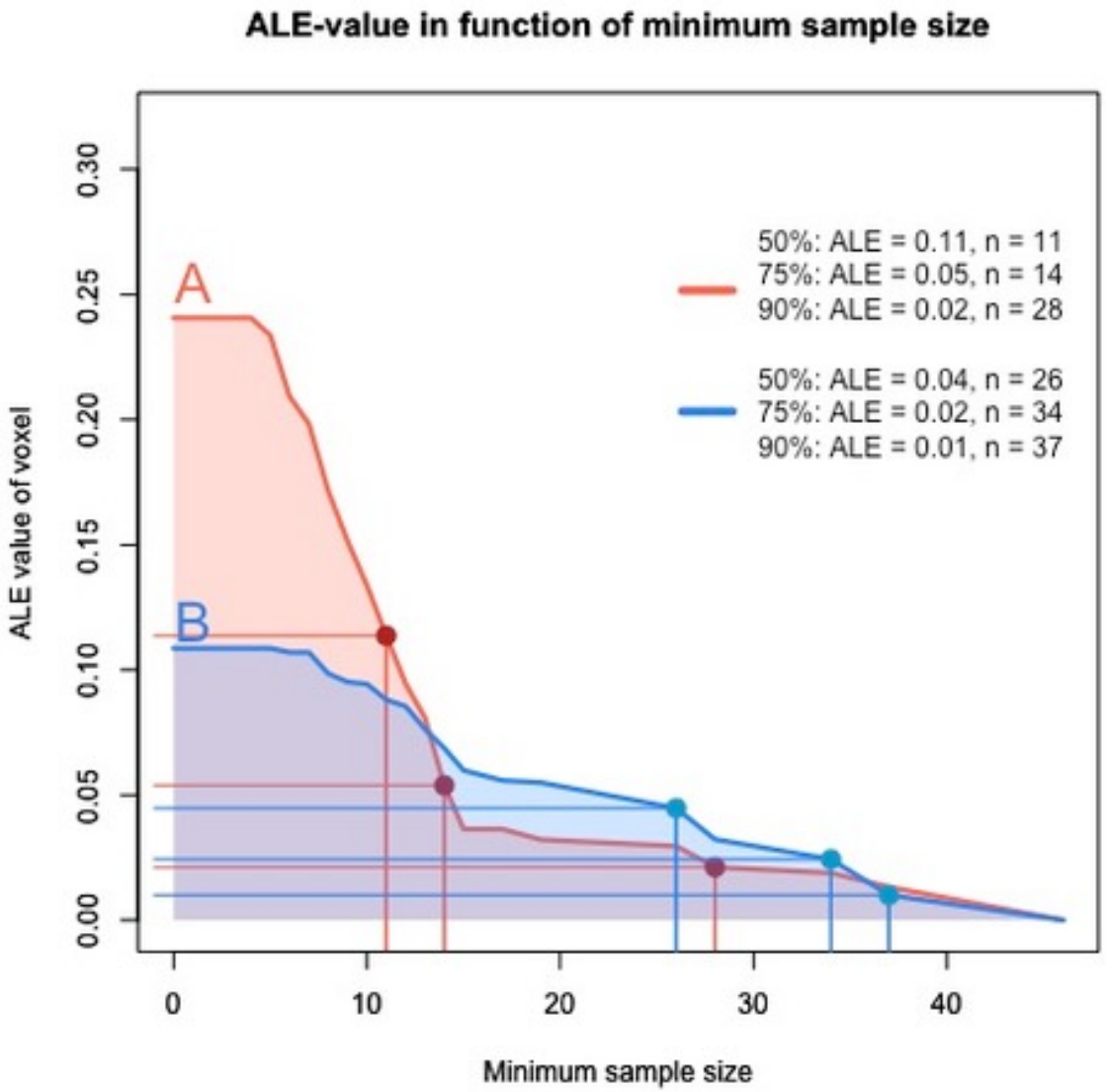


Publication bias



Discussion

- What I did not talk about
  - Bayesian approaches (e.g. Kang et al., 2011)
  - New algorithm for CBMA - clusterZ (Tench et al., 2017)
  - ...
- Challenges (even when input is ideal)
  - Computational challenges
  - Effect sizes (selection bias!)
  - Explain variance between study results
  - Corrections for publication bias

Team

Thank you to all (former) members of our group!

Listed alphabetically:

- Freya Acar
- Han Bossier
- Jasper Degryse
- Joke Durnez
- Ruth Seurinck
- Sanne Roels

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