Overview of Meta-Analysis Approaches

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Neuroimaging Meta-Analysis
OHBM Educational Course

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slides & posters @ **http://warwick.ac.uk/tenichols/ohbm**

Overview

- Non-imaging meta-analysis
- Menu of meta-analysis methods
  - ROI's, IBMA, CBMA
- CBMA details
  - Kernel-based methods – What's in common
  - m/ALE, M/KDA – What's different
- Limitations & Thoughts

Stages of (non-imaging) Meta-Analysis

1. Define review's specific objectives.
2. Specify eligibility criteria.
3. Identify all eligible studies.
4. Collect and validate data rigorously.
5. Display effects for each study, with measures of precision.
6. Compute average effect, random effects std err
7. Check for publication bias, conduct sensitivity analyses.

Jones, D. R. (1995). Meta-analysis: weighing the evidence. *Statistics in Medicine*, 14(2), 137–49.

Methods for (non-imaging) Meta-Analysis (1)

- P-value (or Z-value) combining
  - Fishers (≈ average –log P)
  - Stouffers (≈ average Z)
  - Used only as method of last resort
    - Based on significance, not effects in real units
    - Differing *n* will induce heterogeneity (Cummings, 2004)
- Fixed effects model
  - Requires effect estimates and standard errors
    - E.g. Mean survival (days), and standard error of mean
  - Gives weighted average of effects
    - Weights based on per-study standard errors
  - Neglects inter-study variation

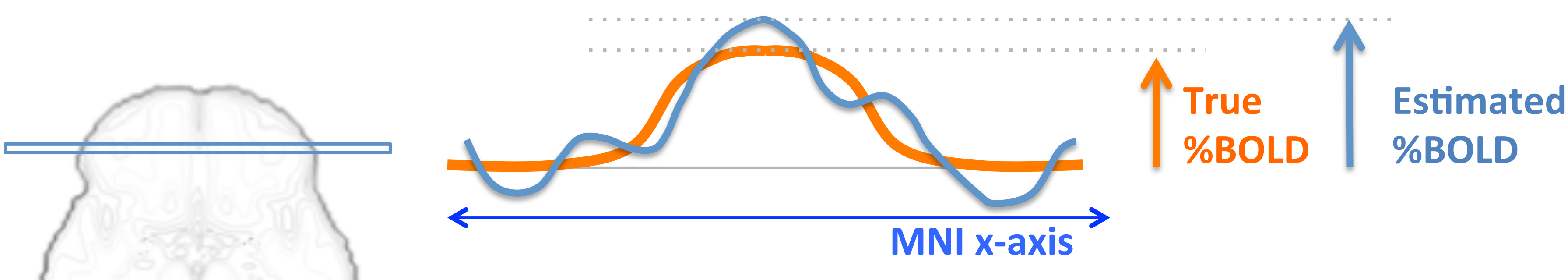
Cummings (2004). Meta-analysis based on standardized effects is unreliable. *Archives of Pediatrics & Adolescent Medicine*, 158(6), 595–7.

Methods for (non-imaging) Meta-Analysis (2)

- Random effects model
  - Requires effect estimates and standard errors
  - Gives weighted average of effect
    - Weights based on per-study standard errors *and* inter-study variation
  - Accounts for inter-study variation
- Meta regression
  - Account for study-level regressors
  - Fixed or random effects

Neuroimaging Meta-Analysis Approaches (1)

- Region of Interest
  - Traditional Meta-Analysis, on mean %BOLD & stderr
  - Almost impossible to do
    - ROI-based results rare (exception: PET)
    - Different ROIs used by different authors
    - Peak %BOLD useless, due to voodoo bias
      - Peak is overly-optimistic estimate of %BOLD in ROI



Neuroimaging Meta-Analysis Approaches (2)

- Intensity-Based Meta-Analysis (IBMA)
  - With P/T/Z Images only
    - Only allows Fishers/Stouffers *Not best practice* ☹
  - With COPE's only
    - Only allows random-effects model without weights
      - Can't weight by sample size! *Not best practice* ☹
  - With COPE's & VARCOPES
    - FSL's FEAT/FLAME ***is*** the random effect meta model!
      - 2^{nd}-level FLAME: Combining subjects
      - 3^{rd}-level FLAME: Combining studies
    - Allows meta-regression *Best practice* ☺
  - But image data rarely shared

Bad practice ☹

Neuroimaging Meta-Analysis Approaches (3)

- Coordinate-Based Meta-Analysis (CBMA)
  - x,y,z locations only
    - Activation Likelihood Estimation (ALE)

      Turkeltaub et al. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *NeuroImage*, 16(3), 765–780.
      Eickhoff et al. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, 30(9), 2907-26.
      Eickhoff et al. (2012). Activation likelihood estimation meta-analysis revisited. *NeuroImage*, 59(3), 2349–61

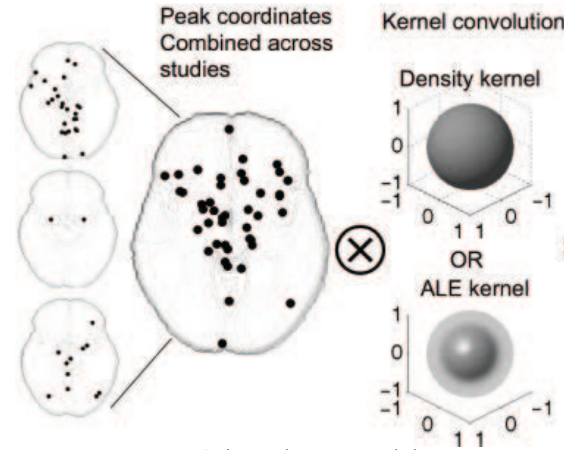
    - Multilevel Kernel Density Analysis (MKDA)

      Wager et al. (2004). Neuroimaging studies of shifting attention: a meta-analysis. *NeuroImage* 22 (4), 1679–1693.
      Kober et al. (2008). Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *NeuroImage*, 42(2), 998–1031.

  - x,y,z and Z-value
    - Signed Difference Mapping (SDM)

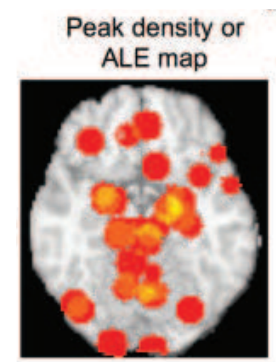
      Radua & Mataix-Cols (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry*, 195:391-400.
      Costafreda et al. (2009). A parametric approach to voxel- based meta-analysis. *NeuroImage*, 46(1):115-122.

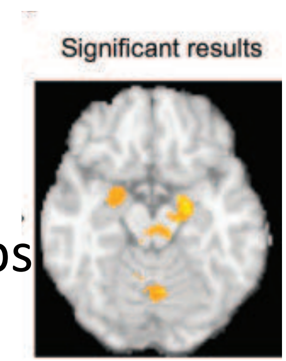
CMBA Kernel Methods



Wager et al. (2007). SCAN, 2(2), 150–8.

- Create study maps
  - Each focus is replaced with kernel
    - Important details on kernel overlap
- Create meta maps
  - Study maps combined
- Inference
  - Traditional voxel-wise or cluster-wise
    - Voxel-wise – FDR or FWE
    - Cluster-wise – FWE
  - Monte Carlo test
    - H_0: no consistency over studies
    - Randomly place each study's foci, recreate meta maps
    - Not actually a permutation test (see Besag & Diggle (1977))

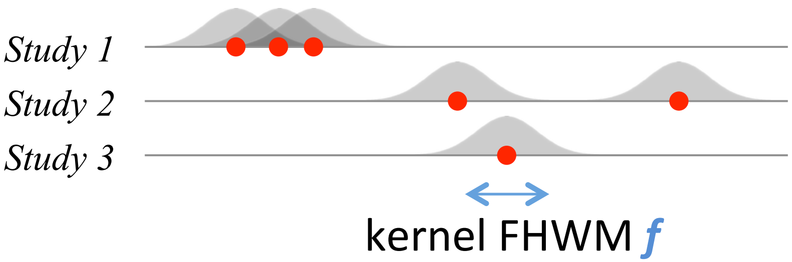


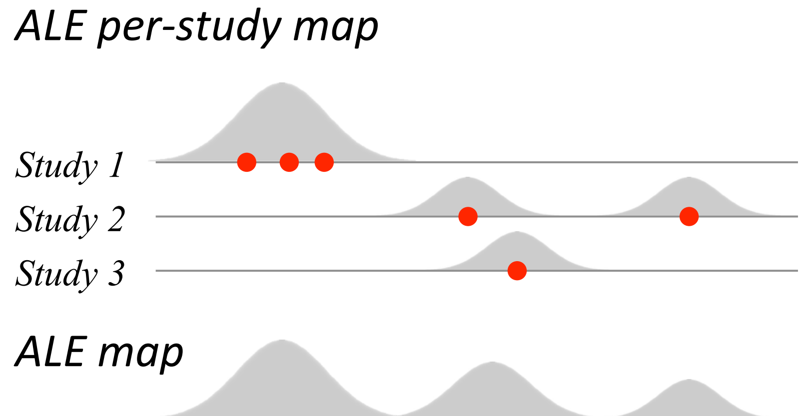


Besag & Diggle (1977). Simple Monte Carlo tests for spatial pattern. *JRSS C (Applied Statistics)*, 26(3), 327–333.

Kernel Methods History – m/ALE

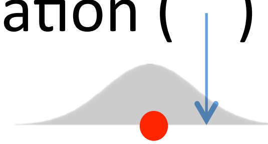
ALE – Activation Likelihood Estimation
(Turkeltaub et al., 2002)





ALE interpretation for single focus (●)

Probability of observing a focus at that location ( )



ALE combining

Probability of union of events…

$$\mathrm{ALE}(p_1,p_2) = p_1 + p_2 - p_1 \times p_2$$

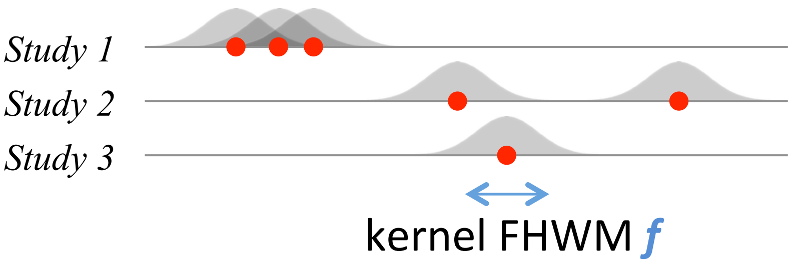
$$\mathrm{ALE}(p_1,p_2,p_3) = p_1 + p_2 + p_3 - p_1 \times p_2 - p_1 \times p_3 - p_2 \times p_3 + p_1 \times p_2 \times p_3$$

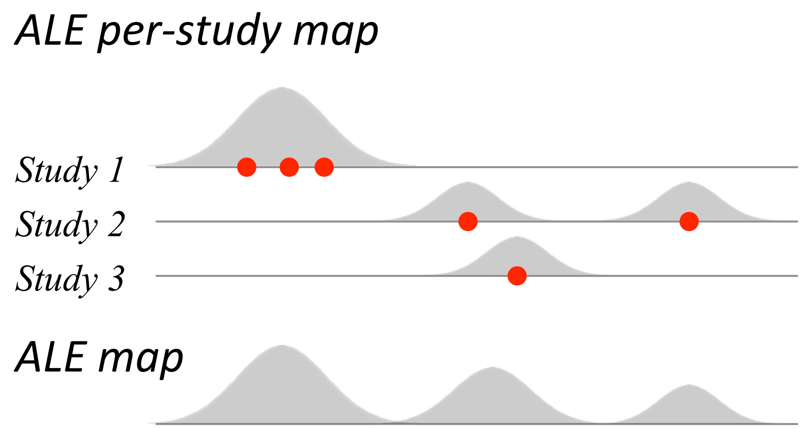
ALE interpretation:

Probability of observing one or more foci at a given location *based* on a model of Gaussian spread with FWHM ***f***

Kernel Methods History – m/ALE

ALE – Activation Likelihood Estimation
(Turkeltaub et al., 2002)

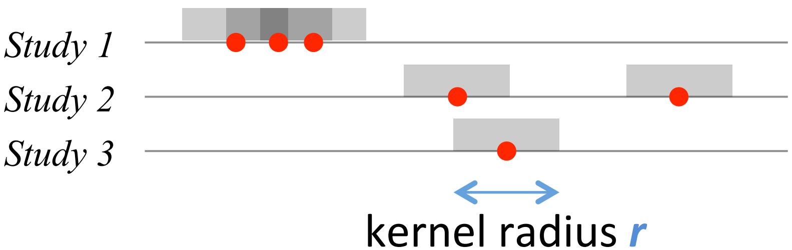




- Problem with first ALE
  - Single study could dominate, if lots one has lots of points
- Modified ALE (Eickhoff et al., 2009; Eickhoff et al., 2012)
  - Revised Monte Carlo test accounts for studies
    - Fix foci, randomly sample each map
  - Adapt kernel size *f* to study sample size
  - Voxel-wise test – no Monte Carlo!
  - Cluster-wise test – still requires Monte Carlo

Kernel Methods History – M/KDA

KDA – Kernel Density Analysis
(Wager et al., 2004)

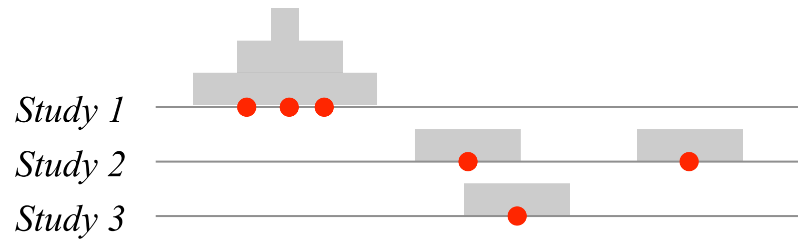


Same problem with individual profligate studies

MKDA (Kober et al., 2008)

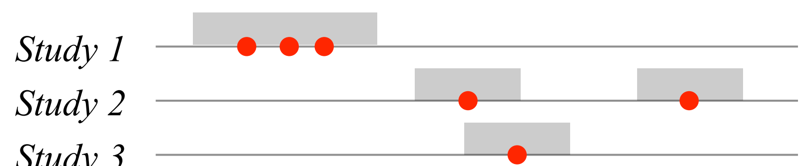
- Truncated kernel
- Monte Carlo test
  - Moves clusters, not individual foci

KDA per-study map



KDA map – average of study maps

MKDA – Multilevel Kernel Density Analysis per-study map



MKDA map – weighted average of study maps

MKDA (unweighted) interpretation:

Proportion of studies having one or more foci within distance *r*

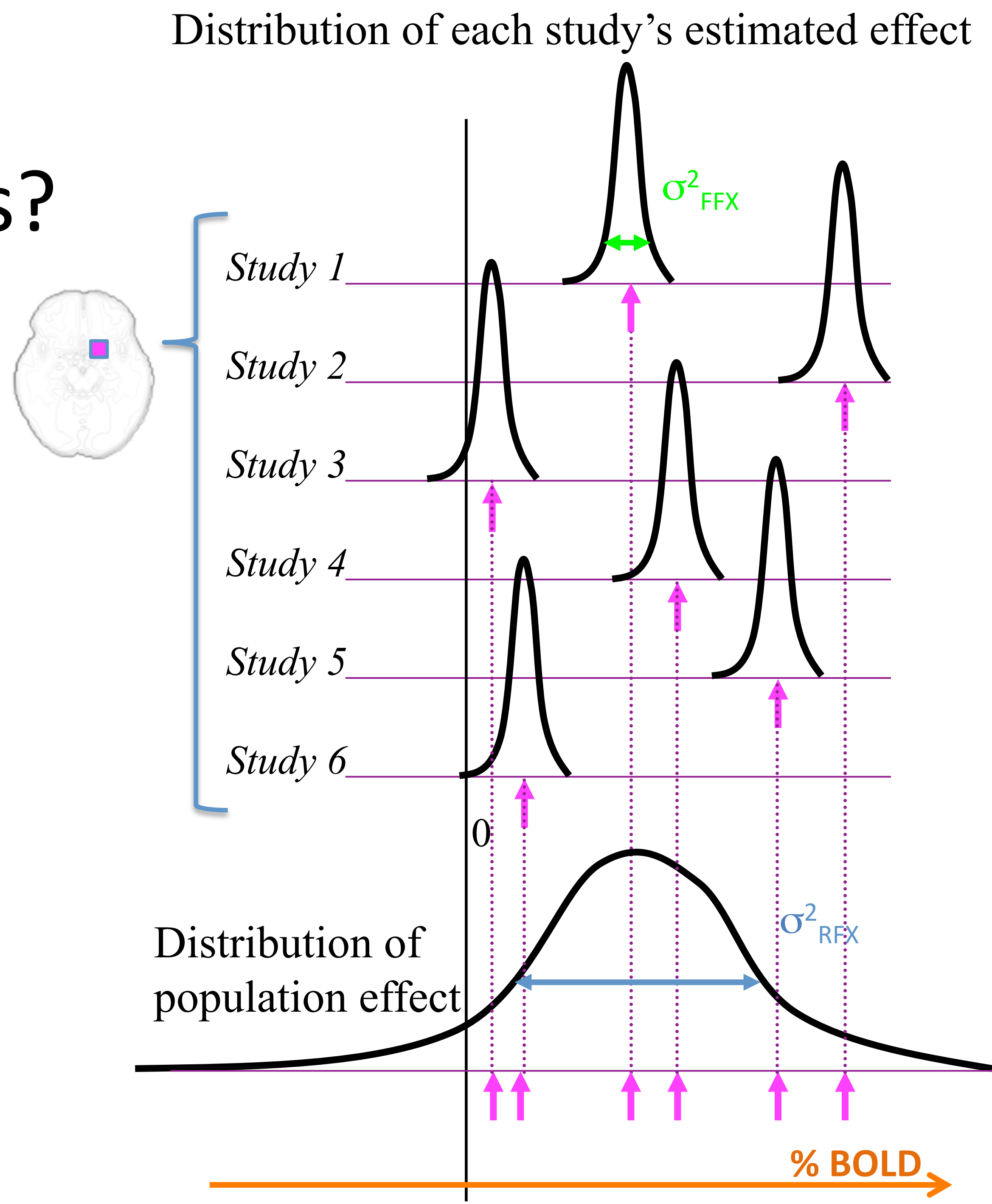
CBMA Limitations

- Effect size
  - Non-imaging MA is all about effect size, CI's
  - What is the effect size?
    - MKDA – Proportion of study result in neighborhood
    - ALE – Probability at individual voxel one or foci
  - Standard errors? CI's?
  - Power/sensitivity
    - 5/10 studies – Great!
    - 5/100 studies – Not great? Or subtle evidence?

- Fixed vs. Random Effects?

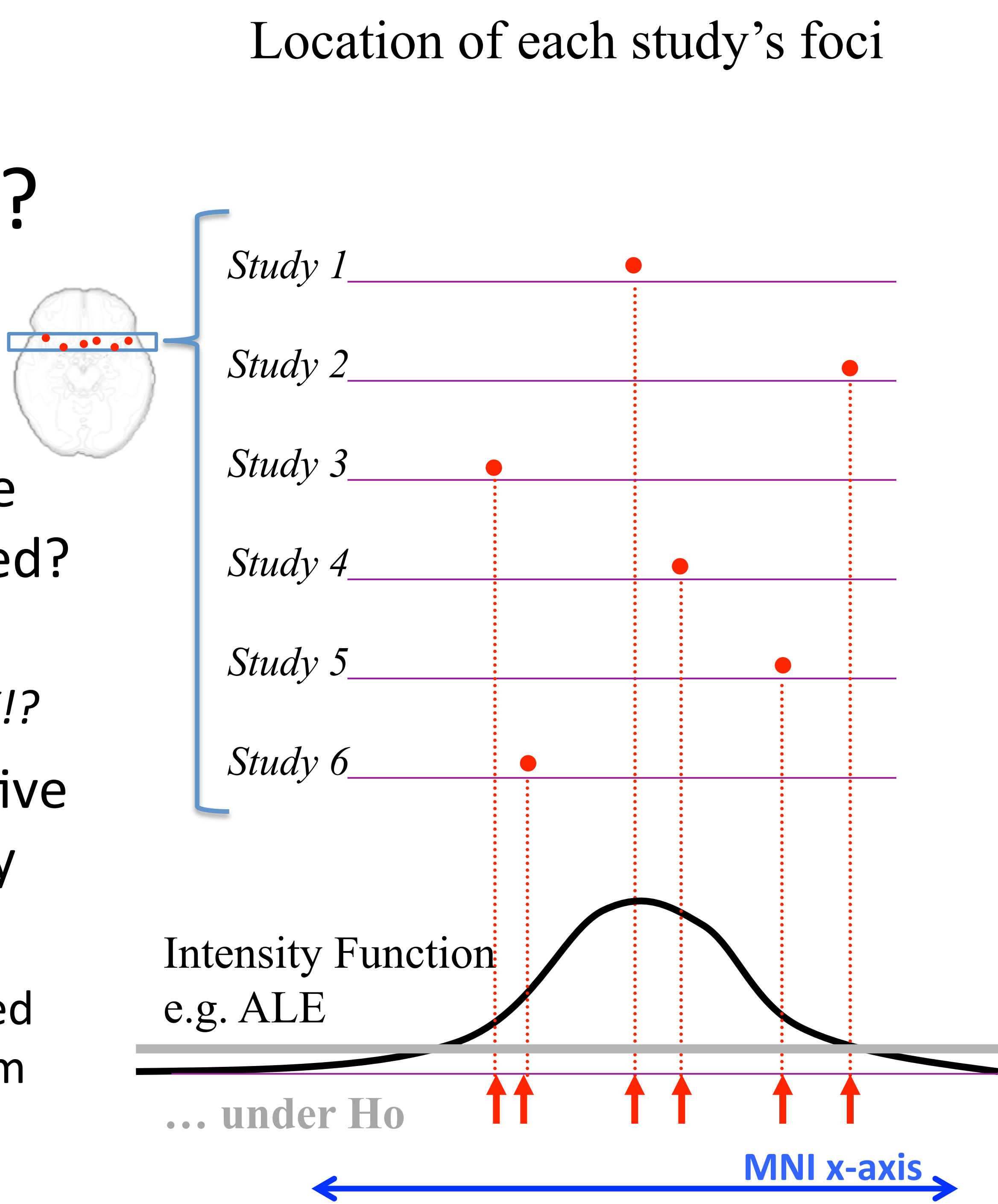
IBMA
Random Effects?

- An effect that generalizes to the population studied
- Significance relative to between-study variation



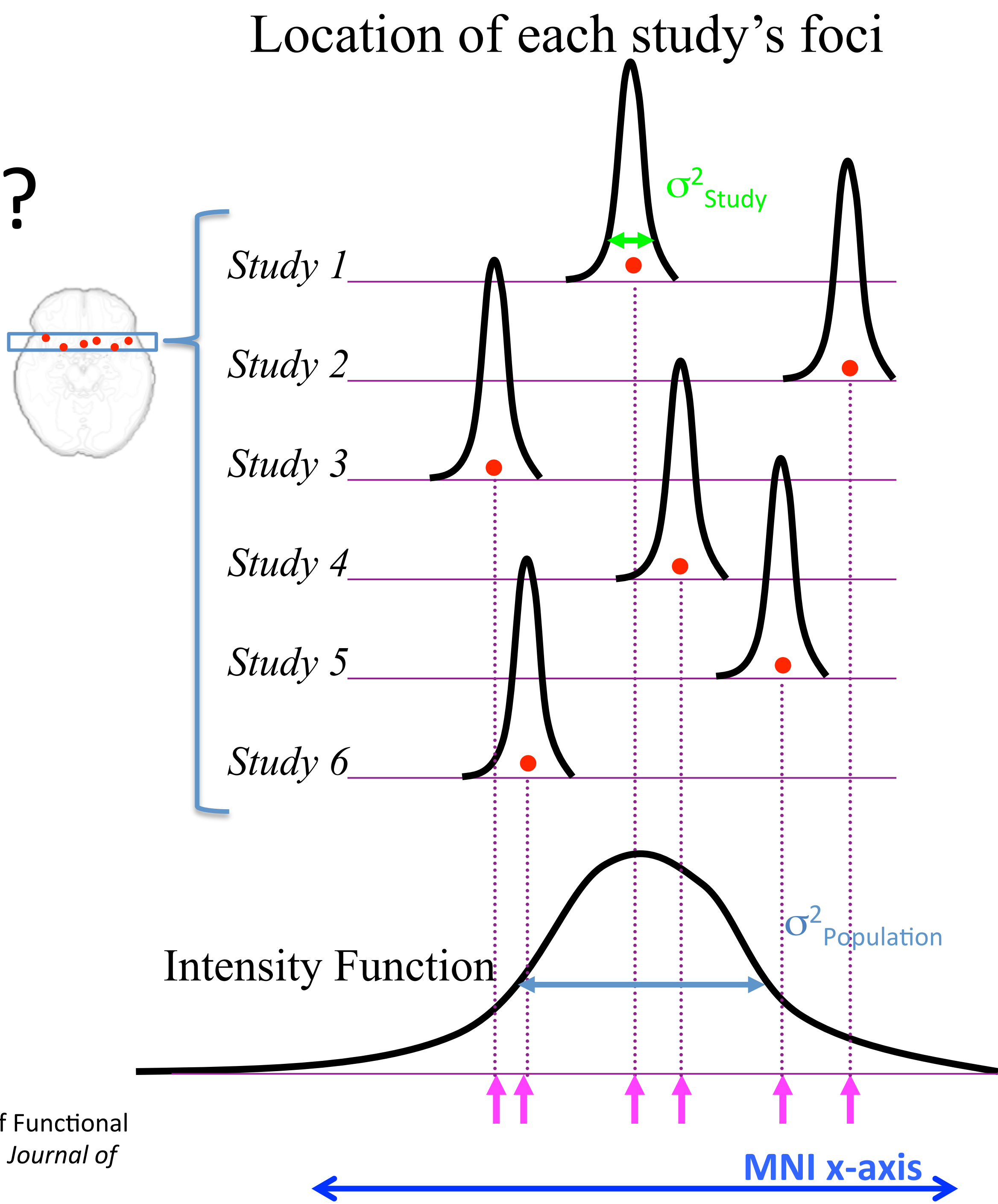
What is a Random Effect?

- CBMA
  - An effect that generalizes to the population studied?
    - *5/10 signif.: OK?*
    - *5/100 signif.: OK!?*
  - Significance relative to between-study variation?
    - Significance based on null of random distribution



What is a Random Effect?

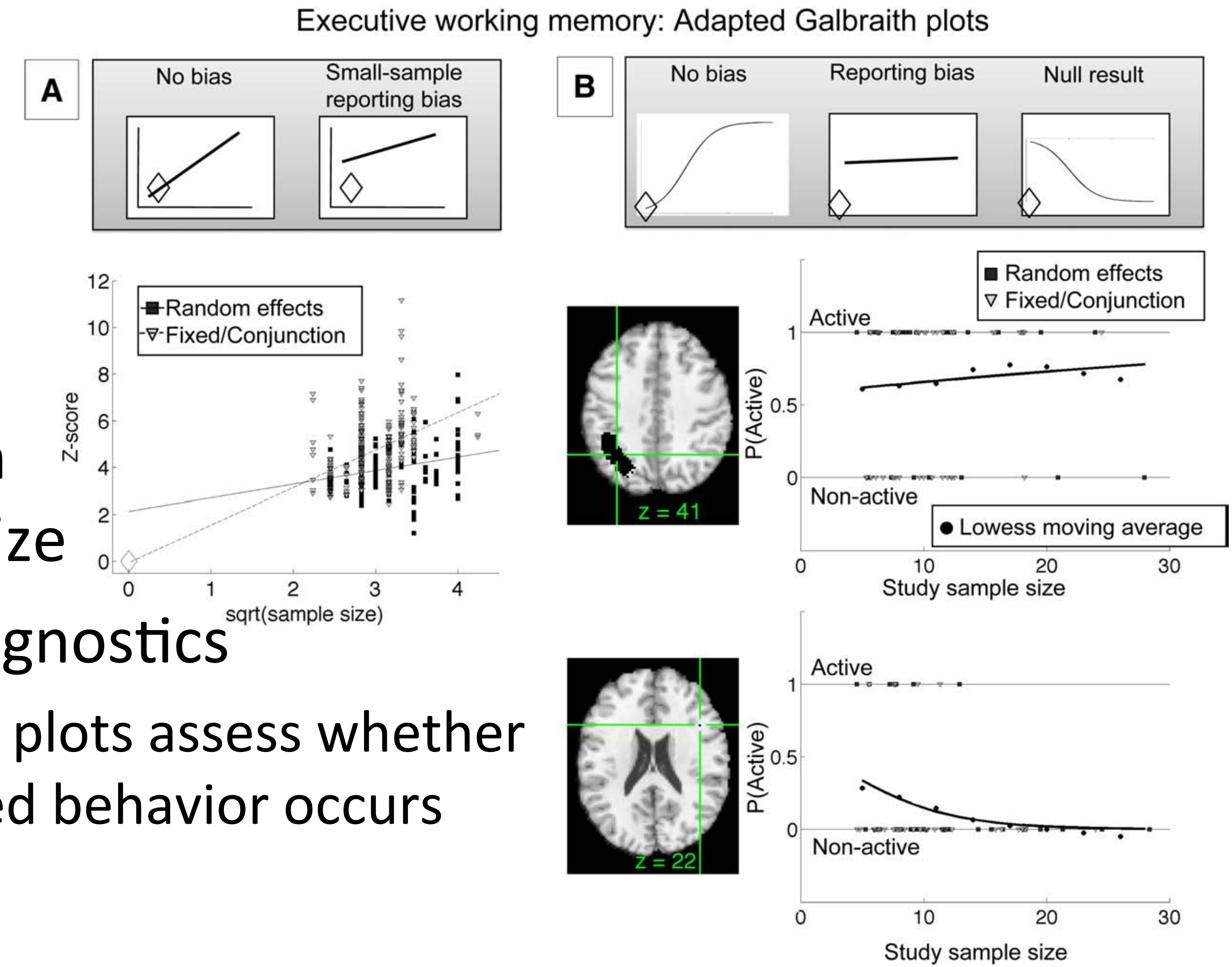
- Bayesian Hierarchical Marked Spatial independent Cluster Process
  - Explicitly parameterizes intra- and inter-study variation



Kang, Johnson, Nichols, & Wage (2011). Meta Analysis of Functional Neuroimaging Data via Bayesian Spatial Point Processes. *Journal of the American Statistical Association*, 106(493), 124–134.

CBMA Sensitivity analyses

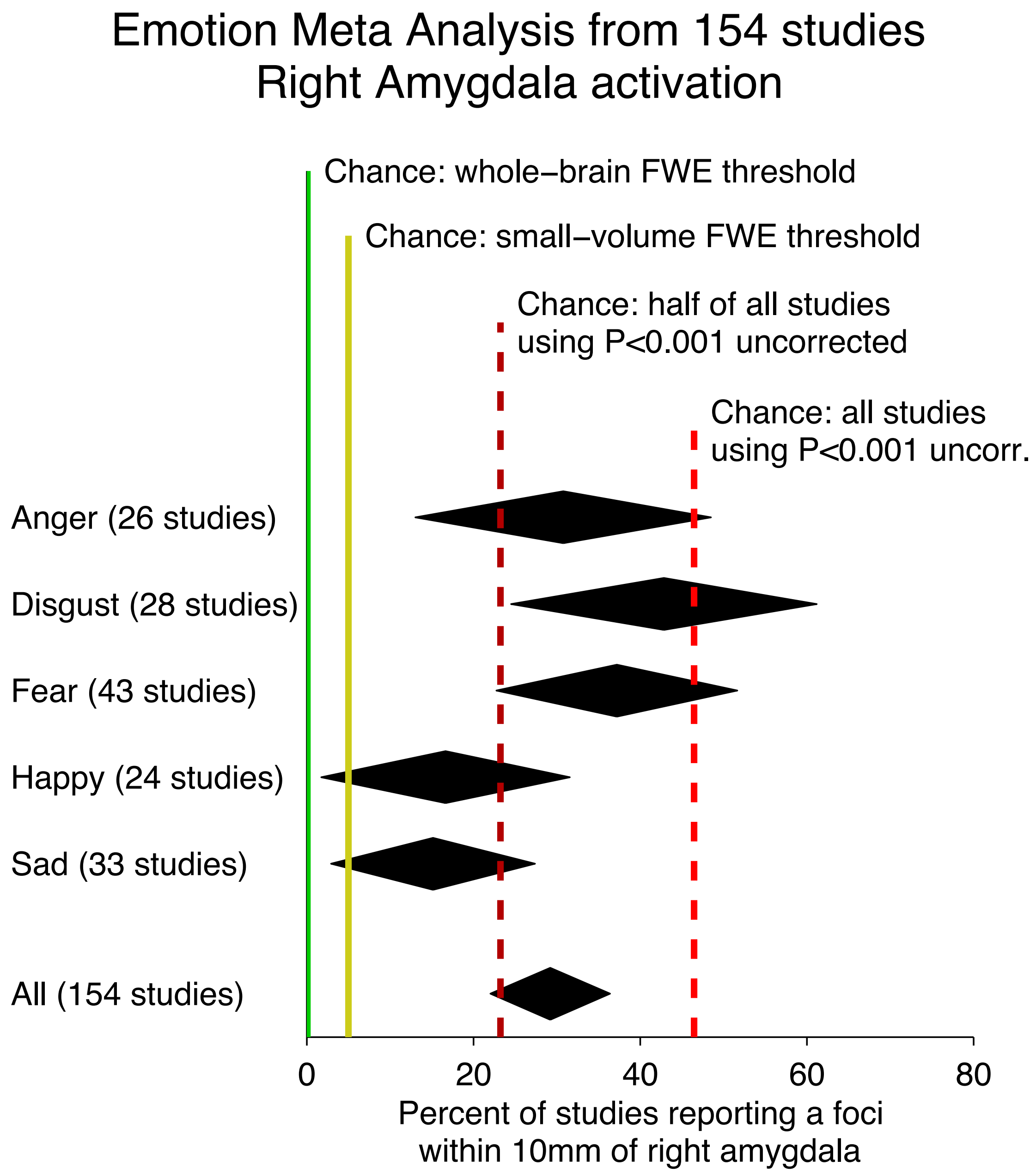
- Z-scores should fall to zero with sample size
- Meta Diagnostics
  - Various plots assess whether expected behavior occurs



Wager et al. (2009). Evaluating the consistency and specificity of neuroimaging data using meta-analysis. *NeuroImage*, 45(1S1), 210–221.

CBMA File Drawer Bias?

- What about "P<0.001 uncorrected" bias?
- Forrest plot
  - MKDA values for right amygdala
  - Can explore different explanations for the effect



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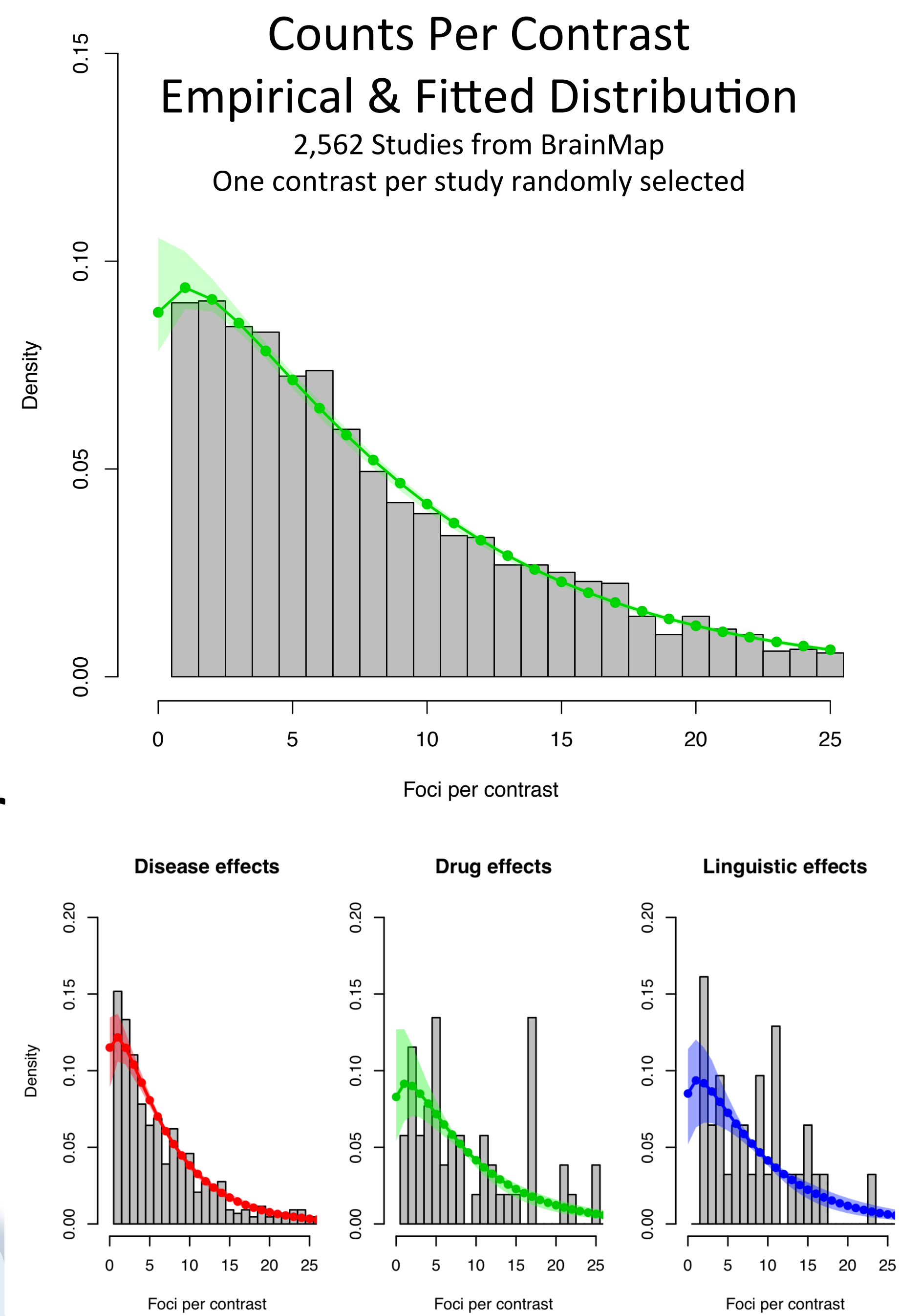
Estimating Size of the File Drawer

- Estimation of “File Drawer” prevalence
- Use foci counts to infer number of missing (0 count) studies
- About 1 study missing per 10 published
  - 9.02 per 100
    95% CI (7.32, 10.72)
  - Varies by subarea



Pantelis Samartsidis, et al. OHBM 2015 Poster 4038-W
“Estimating the prevalence of ‘file drawer’ studies”

Conclusions

- IBMA
  - Would be great, rich tools available
- CBMA
  - 2+ tools available
  - Still lots of work to deliver best (statistical) practice to inferences