

# 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.

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

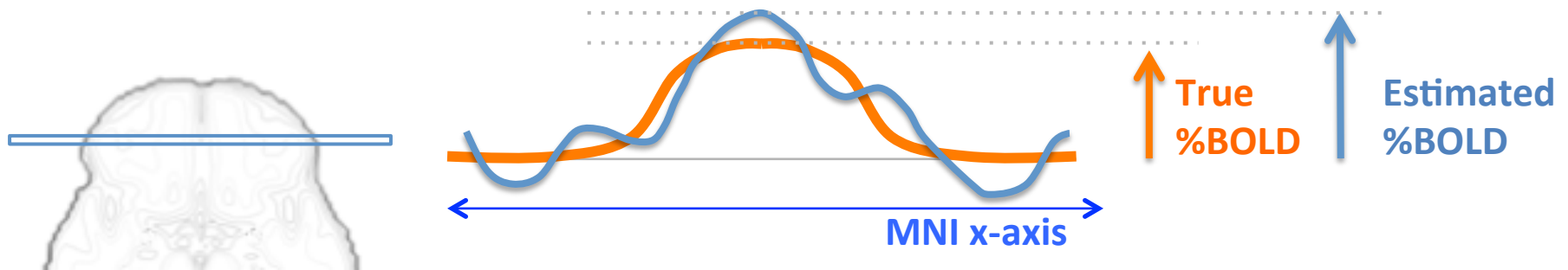
- P-value (or Z-value) combining
  - Fishers ( $\approx$  average  $-\log P$ )
  - Stouffers ( $\approx$  average Z)
  - Used only as method of last resort
    - Based on significance, not effects in real units
    - Differing  $n$  will induce heterogeneity (Cummings, 2004)
- Fixed effects model
  - 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

# 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<sup>nd</sup>-level FLAME: Combining subjects
      - 3<sup>rd</sup>-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)

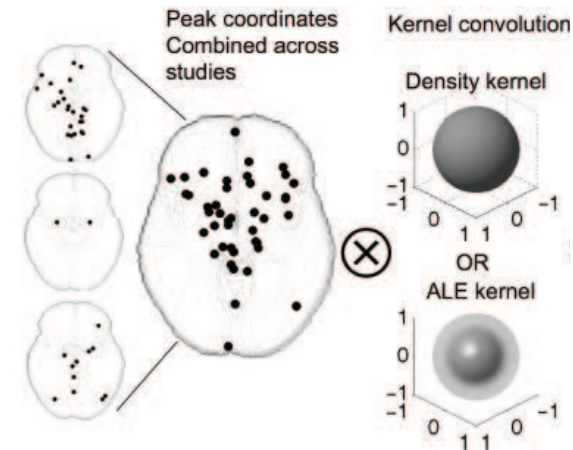
- Radua & Mataix-Cols (2009).** Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry*, 195:391-400.

- Costafreda et al. (2009).** A parametric approach to voxel- based meta-analysis. *NeuroImage*, 46(1):115-122.

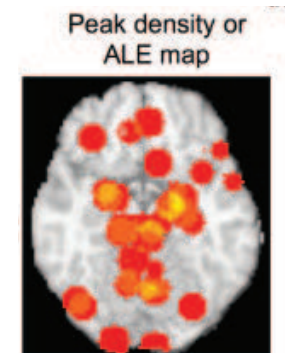


# CMBA Kernel Methods

- 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))

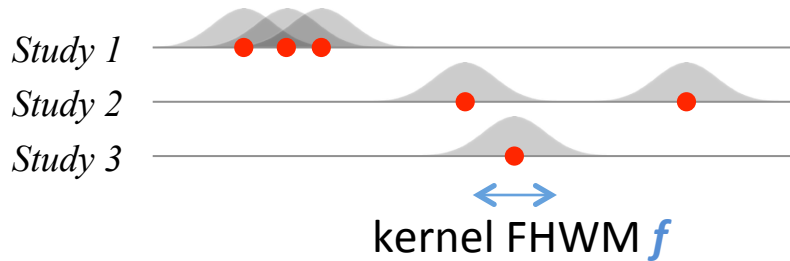


Wager et al. (2007). *SCAN*, 2(2), 150–8.

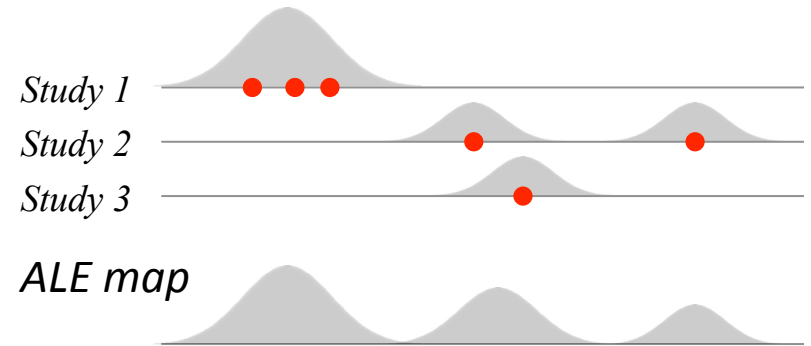


# Kernel Methods History – m/ALE

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



*ALE per-study map*



ALE interpretation for single focus ( ● )

Probability of observing a focus at that location ( )

ALE combining

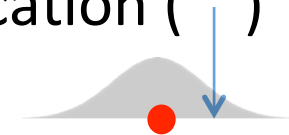
Probability of union of events...

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

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

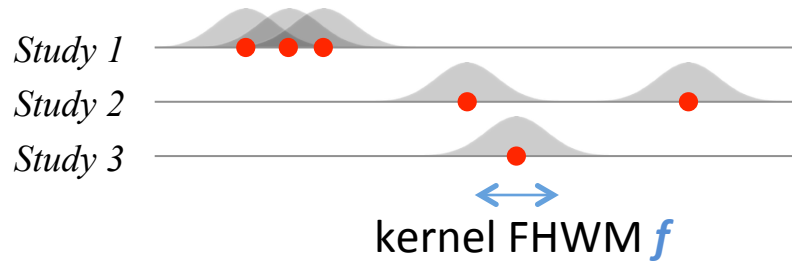
ALE interpretation:

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

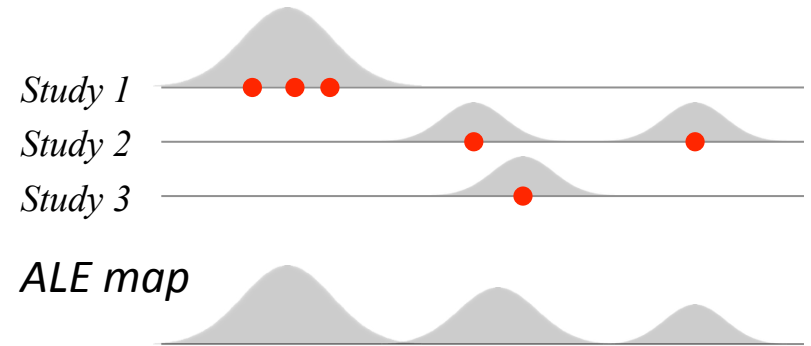


# Kernel Methods History – m/ALE

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



*ALE per-study map*



## 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

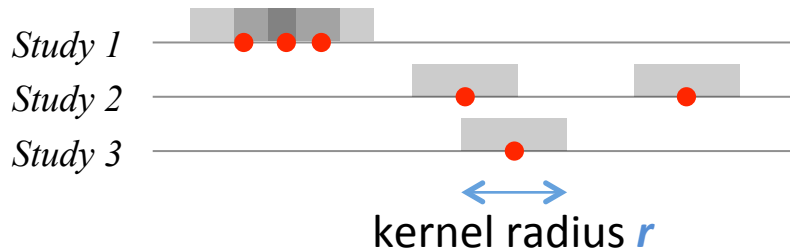
Adapt kernel size  $f$  to study sample size

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

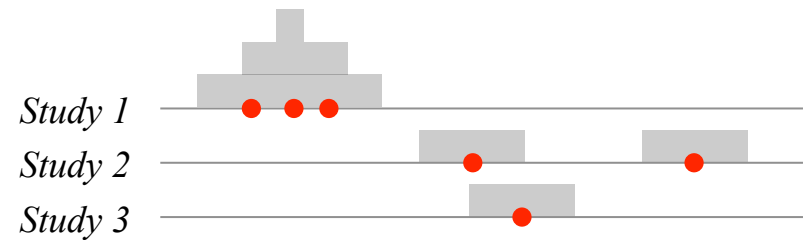
Monte Carlo test

Moves clusters, not  
individual foci

MKDA (unweighted) interpretation:

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

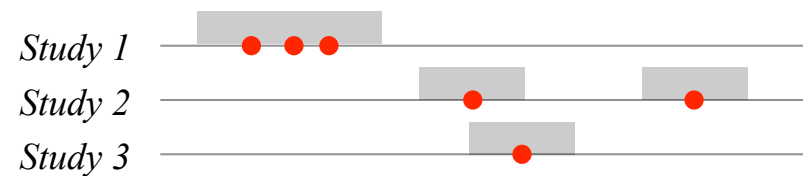
*KDA per-study map*



*KDA map – average of study maps*



*MKDA – Multilevel Kernel Density Analysis  
per-study map*



*MKDA map – weighted average of study maps*



# CBMA Limitations

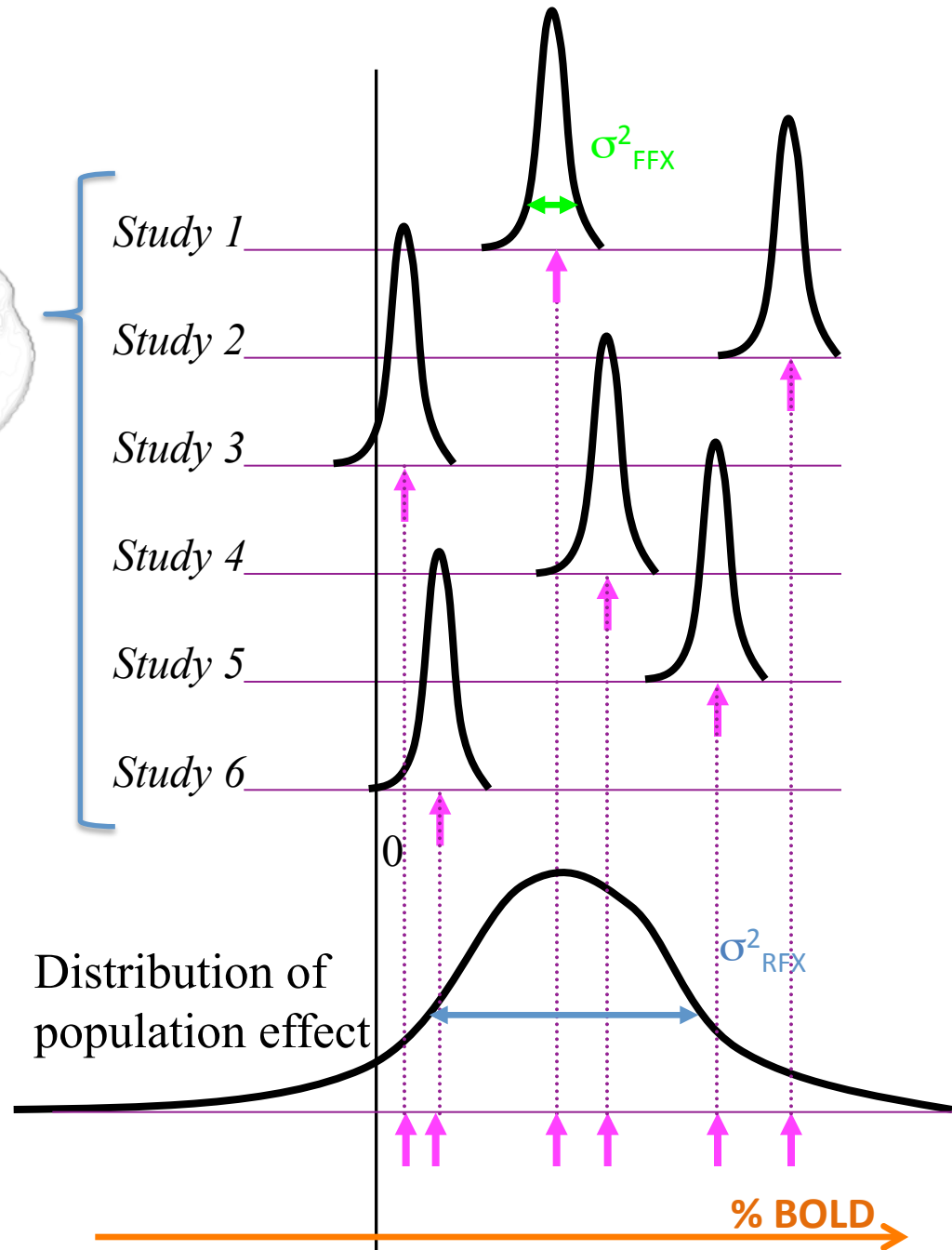
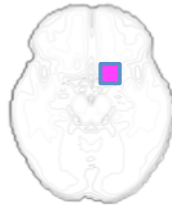
- Effect size
  - Non-imaging MA is all about effect size, CI's
  - What is the effect size?
    - MKDA – Proportion of study result in neighborhood
    - ALE – Probability at individual voxel one or foci
  - Standard errors? CI's?
  - Power/sensitivity
    - 5/10 studies – Great!
    - 5/100 studies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

Distribution of each study's estimated effect

# IBMA

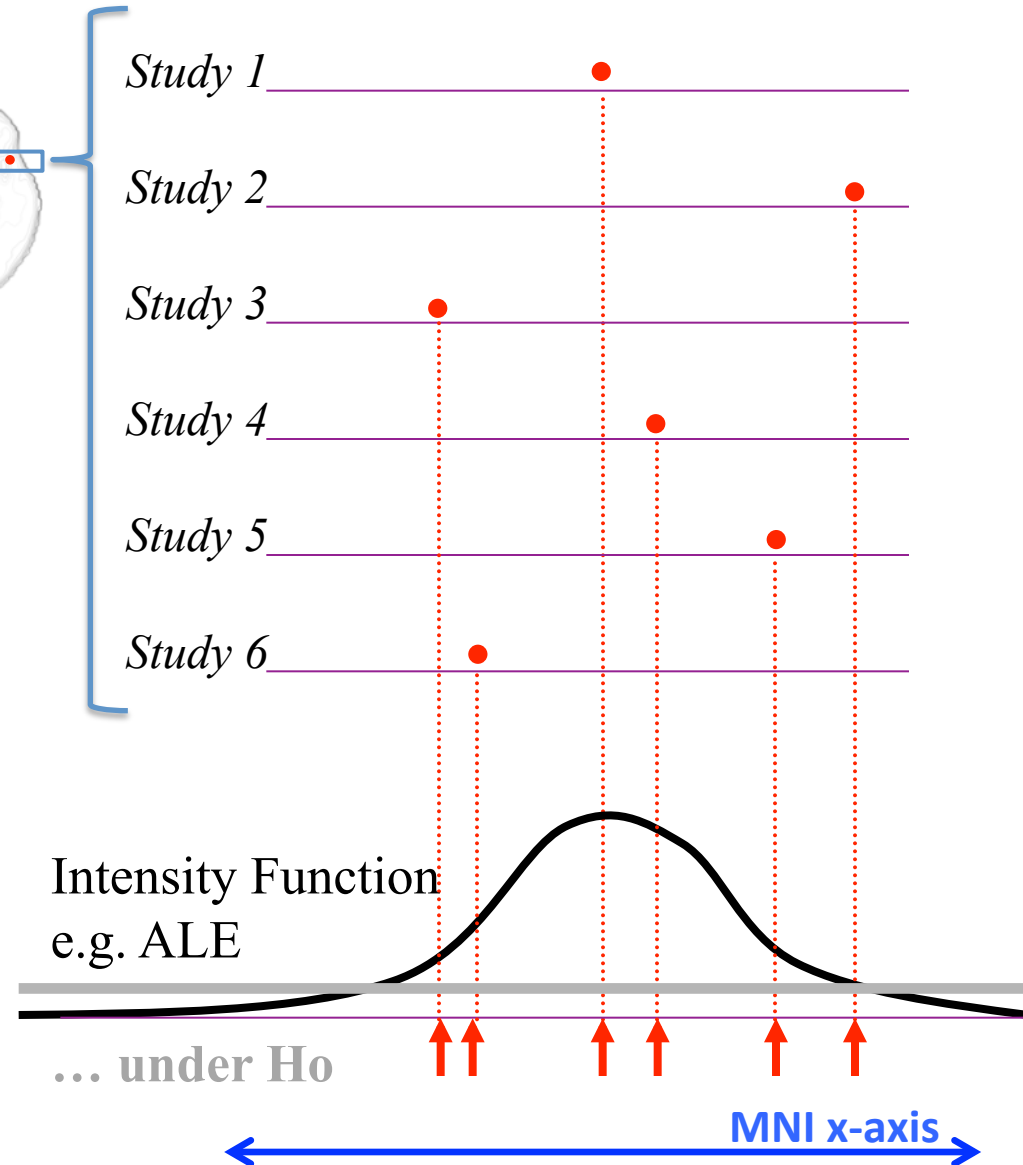
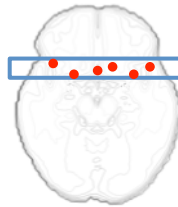
## Random Effects?

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



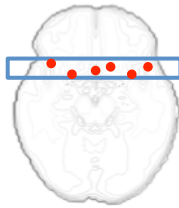
# What is a Random Effect?

- 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

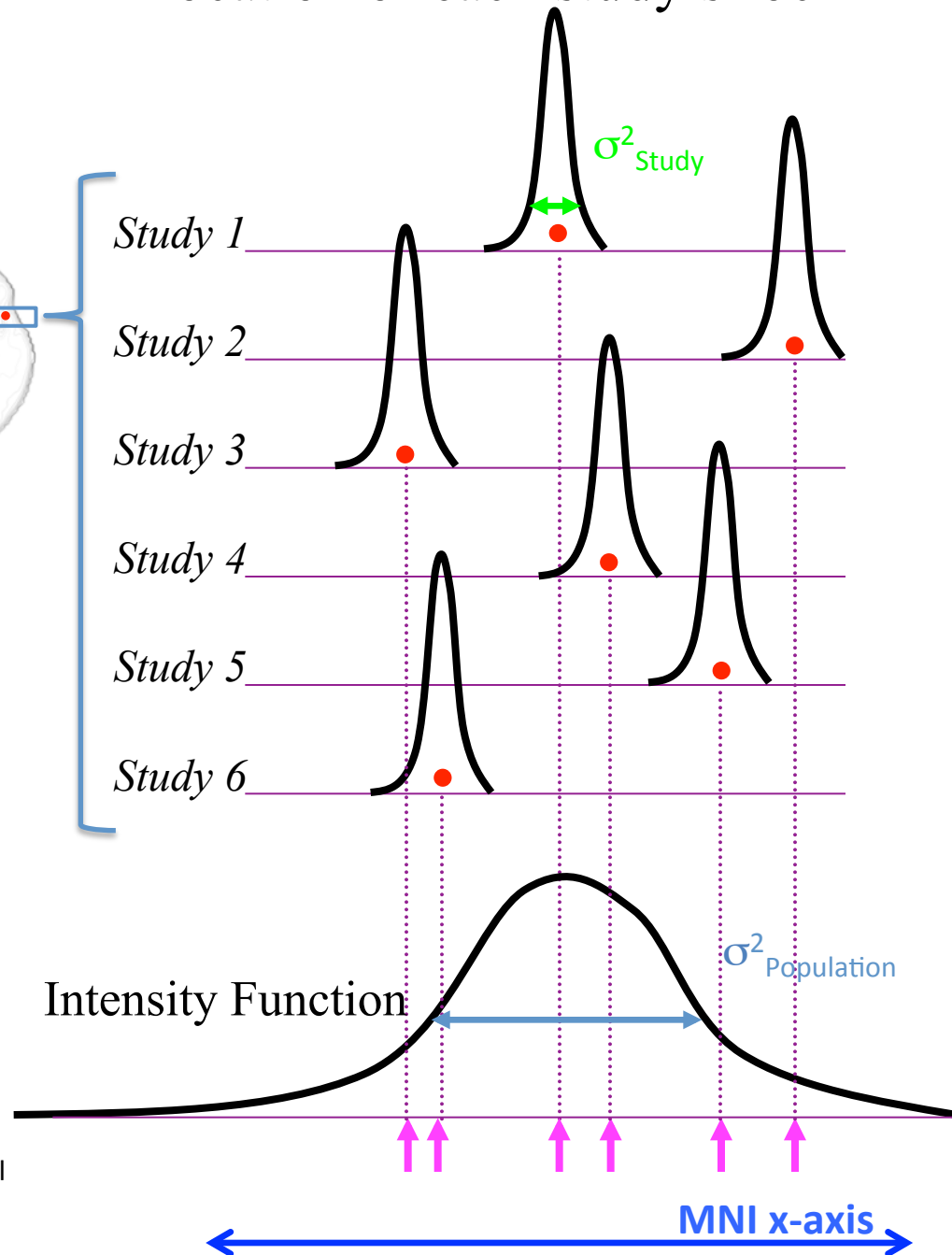


# What is a Random Effect?

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



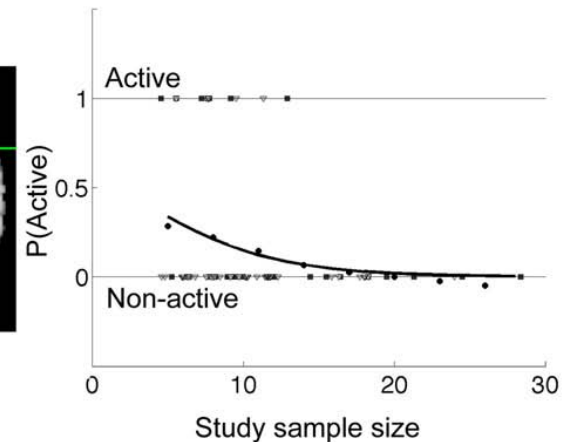
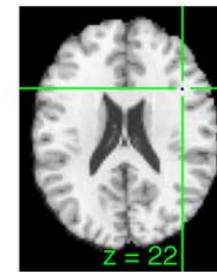
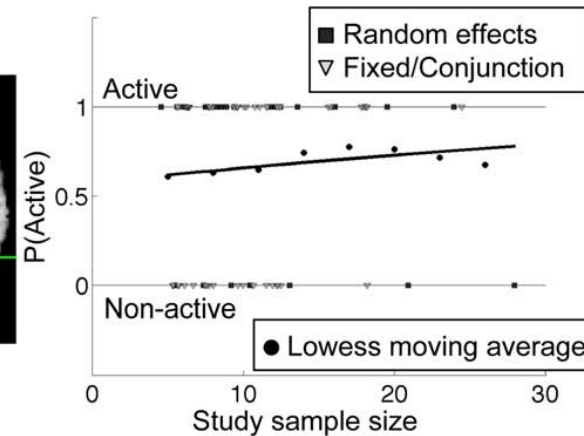
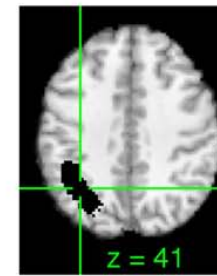
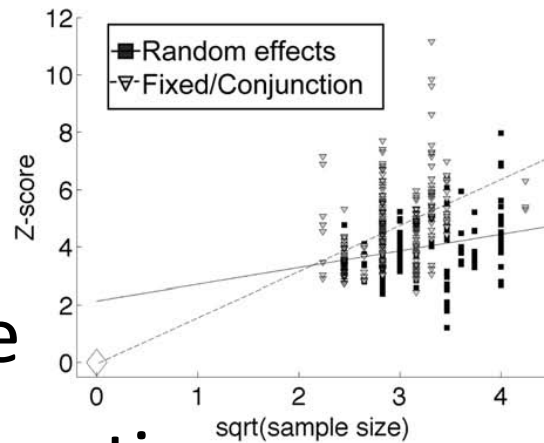
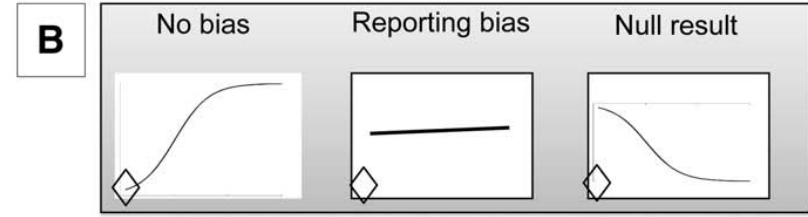
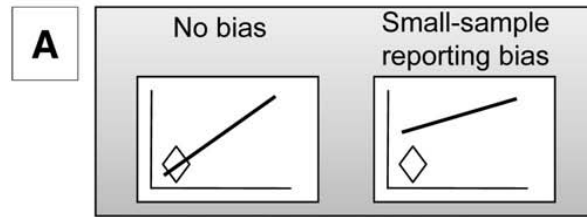
Location of each study's foci





# CBMA Sensitivity analyses

Executive working memory: Adapted Galbraith plots



- Z-scores should fall to zero with sample size

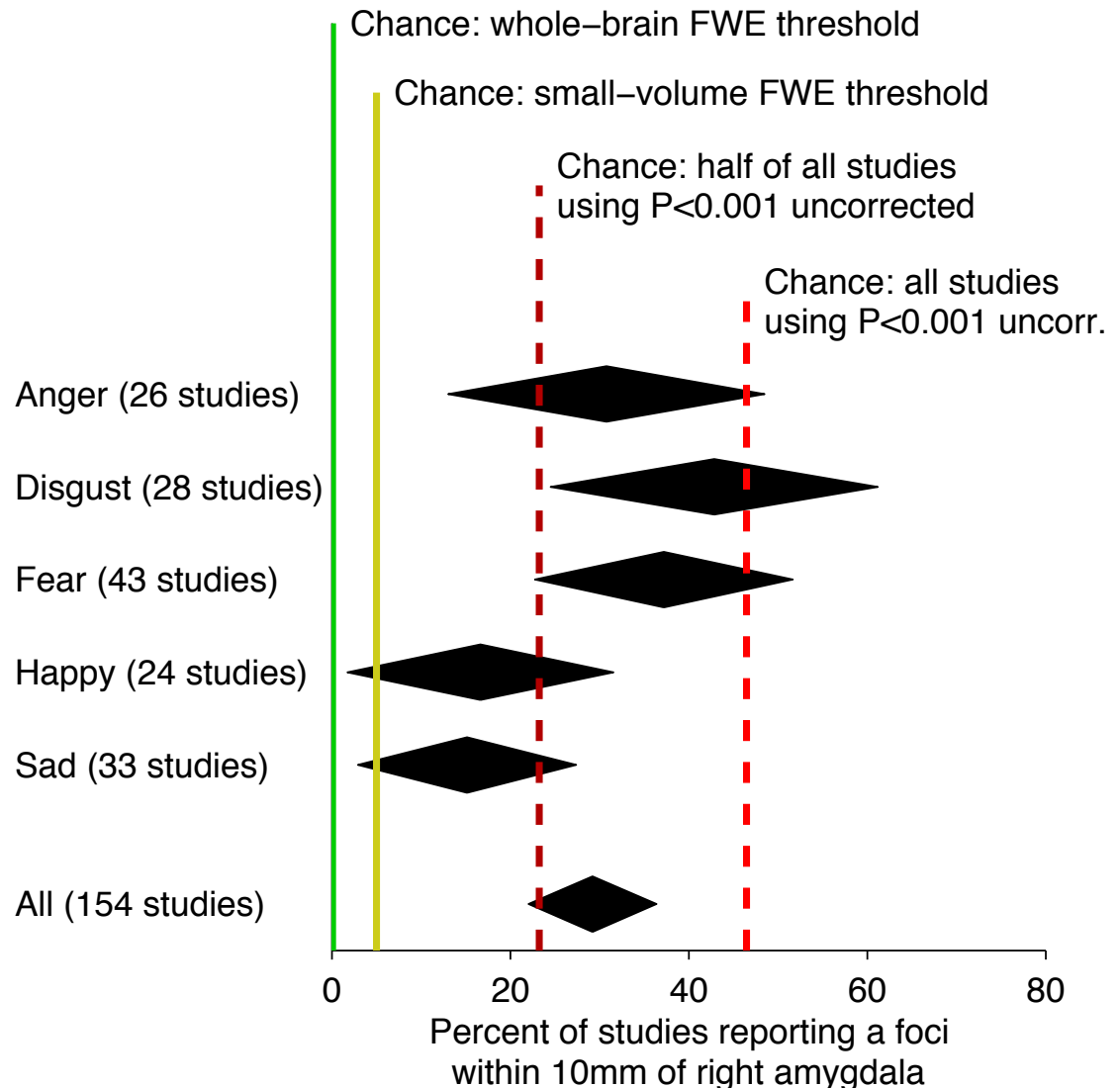
- Meta Diagnostics

- Various plots assess whether expected behavior occurs

# 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

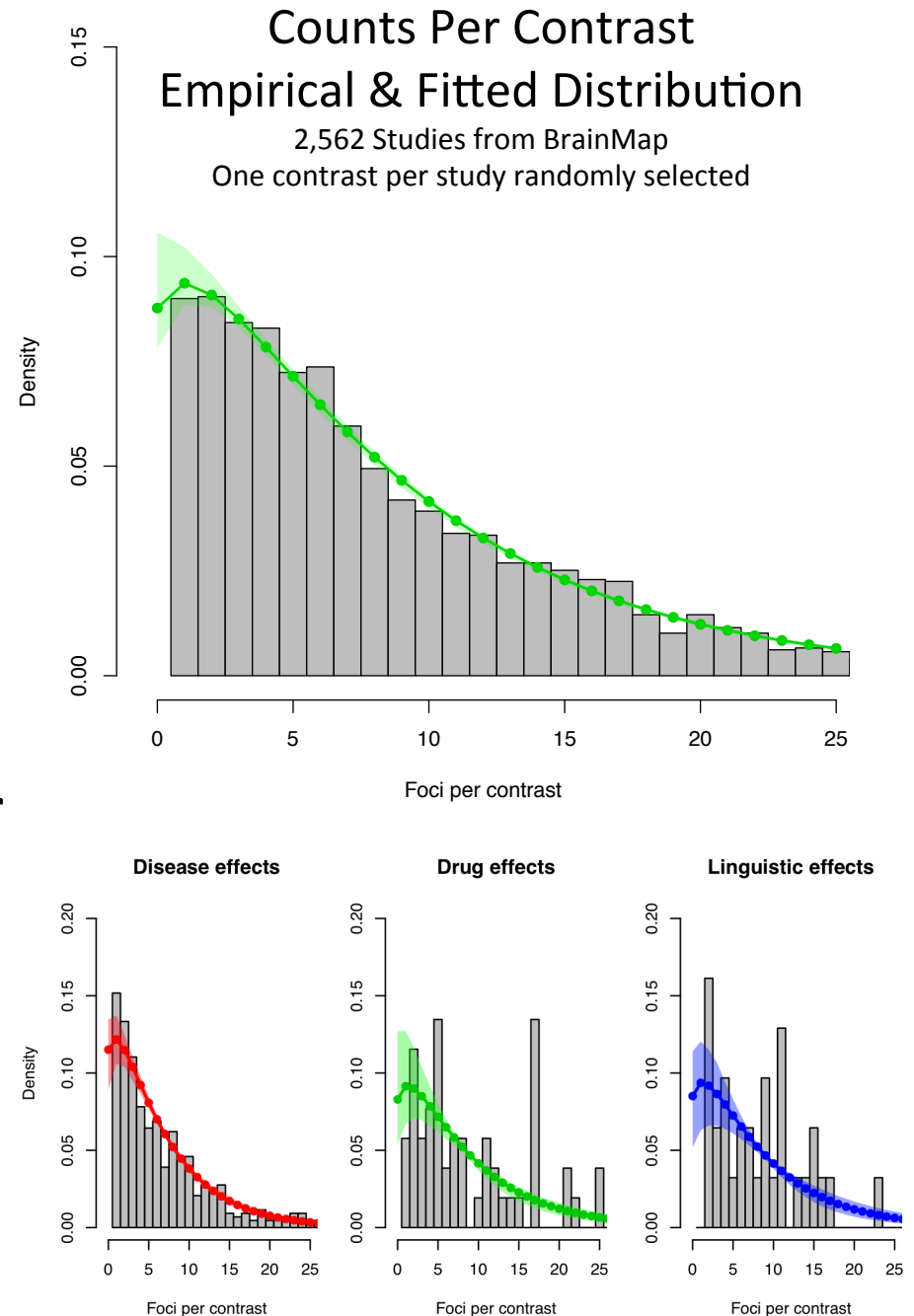
## Emotion Meta Analysis from 154 studies Right Amygdala activation



# Self-Promotion Alert

- 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 Samartidis, et al. 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