Overview of Meta-Analysis Approaches

Thomas E. Nichols
University of Warwick

Neuroimaging Meta-Analysis
OHBM Educational Course

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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 (≈ 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

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
  – With COPE’s only
    • Only allows random-effects model without weights
      – Can’t weight by sample size!
  – With COPE’s & VARCOPES
    • FSL’s FEAT/FLAME *is* the random effect meta model!
      – 2\textsuperscript{nd}-level FLAME: Combining subjects
      – 3\textsuperscript{rd}-level FLAME: Combining studies
    • Allows meta-regression
  – But image data rarely shared

Best practice 😊
Not best practice 😞
Not best practice 😞
Bad practice 😞
Neuroimaging Meta-Analysis Approaches (3)

• Coordinate-Based Meta-Analysis (CBMA)
  – x,y,z locations only

  • Activation Likelihood Estimation (ALE)


  • Multilevel Kernel Density Analysis (MKDA)


  – x,y,z and Z-value

• Signed Difference Mapping (SDM)


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))

Kernel Methods History – m/ALE

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

**ALE per-study map**

**ALE map**

**ALE interpretation for single focus (●)***
Probability of observing a focus at that location (●)

**ALE combining**
Probability of union of events...

\[
ALE(p_1,p_2) = p_1 + p_2 - p_1 \times p_2
\]

\[
ALE(p_1,p_2,p_3) = p_1 + p_2 + p_3 - p_1 \times p_2 - p_1 \times p_3 - p_2 \times p_3 + p_1 \times p_2 \times p_3
\]

**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**

Study 1
Study 2
Study 3

kernel FHWM $f$

**ALE 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)

KDA per-study map

Study 1
Study 2
Study 3

KDA map – average of study maps

MKDA (Kober et al., 2008)

MKDA per-study map

Study 1
Study 2
Study 3

MKDA map – weighted average of study maps

MKDA

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

Location of each study’s foci

Study 1
Study 2
Study 3
Study 4
Study 5
Study 6

Intensity Function
  e.g. ALE

... under Ho
What is a Random Effect?

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

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

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

Emotion Meta Analysis from 154 studies
Right Amygdala activation

- Chance: whole–brain FWE threshold
- Chance: small–volume FWE threshold
- Chance: half of all studies using P<0.001 uncorrected
- Chance: all studies using P<0.001 uncorr.

Percent of studies reporting a foci within 10mm of right amygdala

Anger (26 studies)
Disgust (28 studies)
Fear (43 studies)
Happy (24 studies)
Sad (33 studies)
All (154 studies)
Conclusions

• IBMA
  – Would be great, rich tools available

• CBMA
  – 2+ tools available
  – Still lots of work to deliver best (statistical) practice to inferences