Practical Image-Based Meta-Analysis

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OHBM Neuroimaging Meta-Analysis
Educational course
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THE UNIVERSITY OF WARWICK

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

Agenda

- Meta-analyses in Neuroimaging
  - Neuroimaging study
  - Why meta-analysis?
  - Coordinate-Based and Image-Based
- Image-Based Meta-Analysis
  - Gold standard
  - Other approaches
- Validity of IBMA approaches in neuroimaging

Meta-analysis gold standard

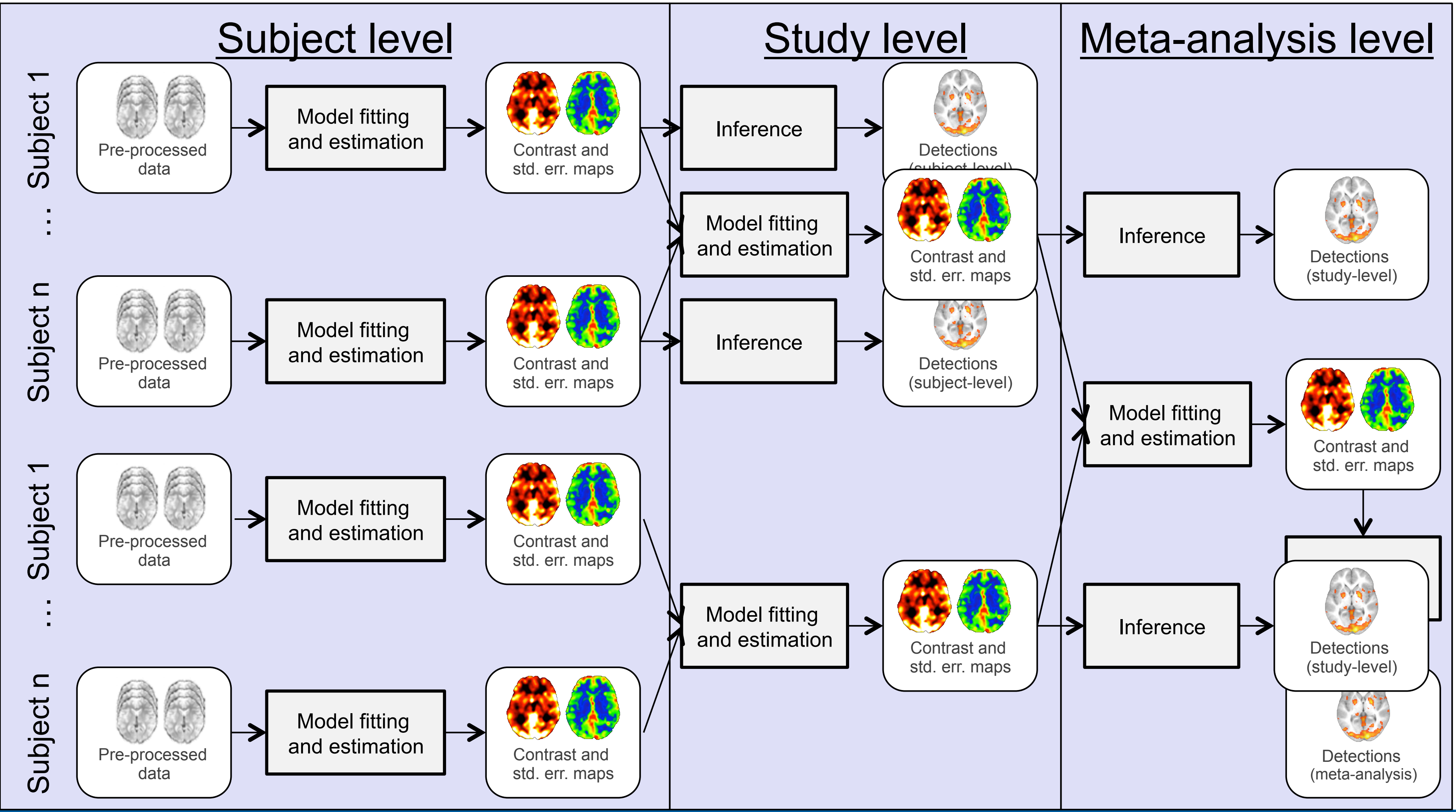
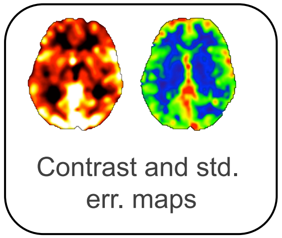


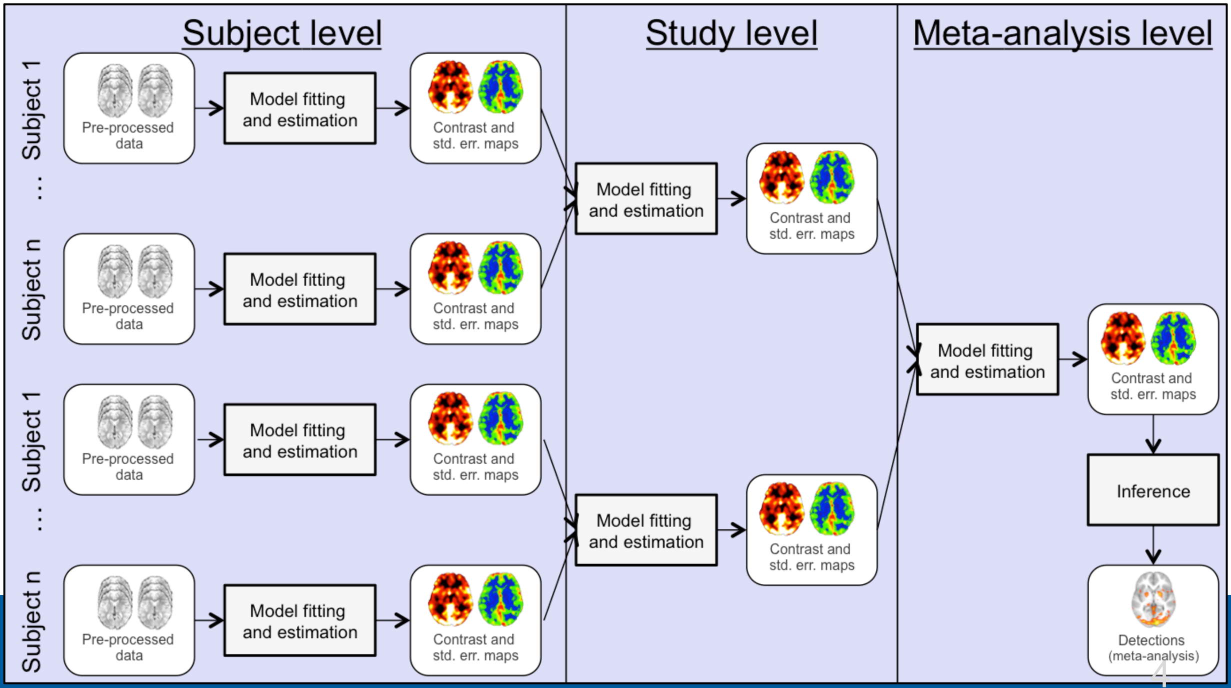
Image-Based Meta-analysis

- Gold standard:

  Third-level Mixed-Effects GLM



- Requirements
  - study-level **Contrast estimates** and **Standard error** maps.
  - Same **units**



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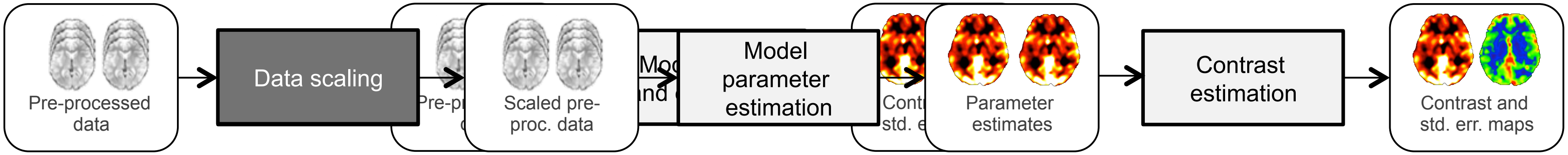
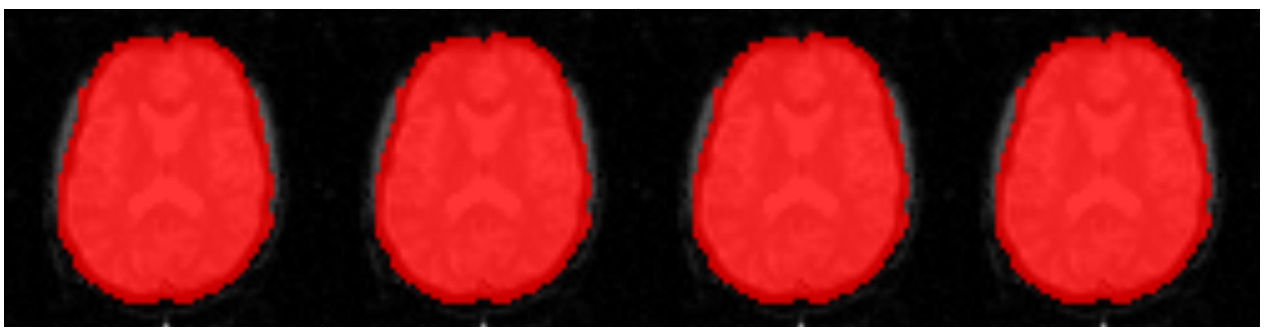
Units of contrast estimates



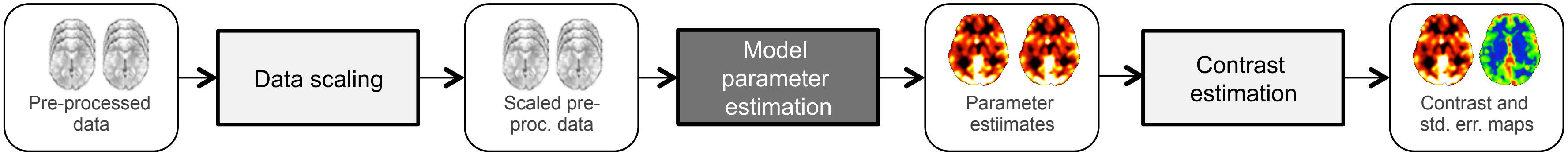
- Data scaling
  - BOLD signal is not quantitative
  - Use “% BOLD” as units

$$scaled\_data = \frac{data * 100}{mean}$$



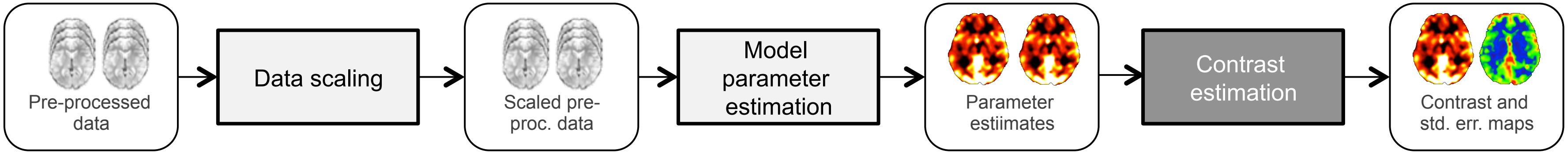
- Dependent on mean estimation (mask, method) and scaling target (100, 10000)

Units of contrast estimates



- Model Parameter Estimation
  - Explain the data as a linear combination of explanatory variables (task, age, motion…)
- Dependent on scaling of explanatory variables.
  – Fix amplitude to 1 for block designs
  – Much more complicated for event related

Units of contrast estimates

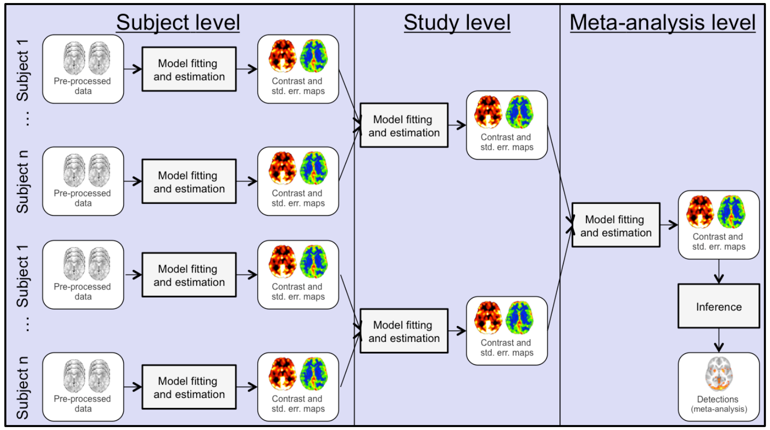


- Contrast Estimation
  - Linear combination of parameter estimates
  - Final statistics invariant to scale
    - e.g. [1 1 1 1] gives same T's & P's as [¼ ¼ ¼ ¼]
- Rule for contrasts to preserve units
  - Positive elements sum to 1
  - Negative elements sum to -1

Image-based Meta-analysis

- Gold standard:

Third-level Mixed-Effects GLM



- But…
  - Units will depend on:
    - The scaling of the data (subject-level)
    - The scaling of the predictor(s) that are involved in the selected contrast (subject- and study-level)
    - The scaling of the selected contrast (subject- and study-level).
  - Contrast estimates and standard error maps are rarely shared…

Image-Based Meta-Analysis Options

- Other statistics available…based on Z's alone
- Fishers's

$$-2 \sum_k \log P_k \sim \chi^2_{2k}$$

  - Sum of −log P-values (from T/Z's converted to P's)
- Stouffer's

$$\sqrt{K} \times \frac{1}{K} \sum_k Z_k \sim \mathcal{N}(0,1)$$

  - Average Z, rescaled to N(0,1)
- "Stouffers's Random Effects (RFX)"

$$\frac{1}{K} \sum_k c\hat{\beta}_k \sim \mathcal{N}(0, \sigma^2_{\mathrm{RFX}})$$

  - Submit Z's to one-sample t-test

Image-Based Meta-Analysis Options

- Other statistics… based on Z's + N's
- Weighted Stouffer's

$$\sum_k w_k Z_k \sim \mathcal{N}(0,1), \quad w_k \propto \sqrt{N_k}$$

  – Z's from bigger studies get bigger weight

Image-Based Meta-Analysis Options

- Other stats… based on contrast estimates only
- Random Effects (RFX) GLM

$$\frac{1}{K}\sum_k c\hat{\beta}_k \sim \mathcal{N}(0, \sigma^2_{\mathrm{RFX}})$$

  – Analyze per-study contrasts as “data”
- … based on contrast estimates and SE’s
- Fixed-Effects (FFX) GLM

$$\frac{1}{K}\sum_k \hat{\theta}_k \sim \mathcal{N}(0, \sum_k \sigma^2_{\mathrm{FFX},k}/K^2)$$

  – *Don’t* estimate variance, just take from first level

Image-Based Meta-Analysis In practice!

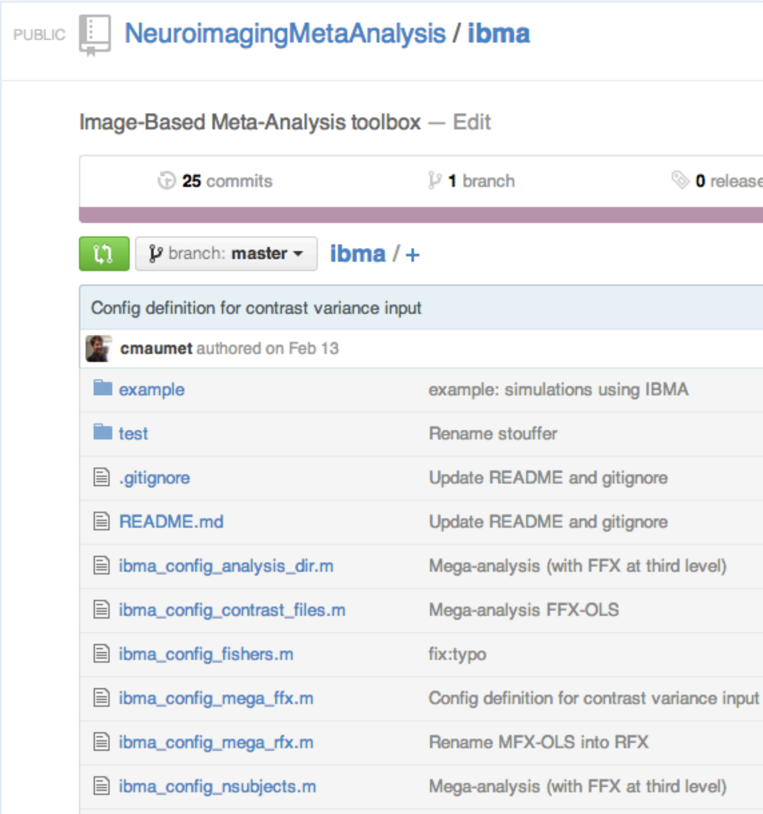
- Not all of these options are easily used

Meta-Analysis Method	Inputs	Neuroimaging Implementation
'Gold Standard' MFX	Con's + SE's	FSL's FEAT SPM spm_mfx
RFX GLM Stouffer's RFX	Con's Z's	FSL, SPM, AFNI, etc…
FFX GLM Fisher's Stouffer's Stouffer's Weighted	Con's +SE's Z's Z's Z's + N's	n/a

Self Promotion Alert: IBMA toolbox

- SPM Extension
- Produces IBMA inferences using permutation/SnPM
- Still in beta!
  - But welcome all feedback
- Available on github:

https://github.com/NeuroimagingMetaAnalysis/ibma



Meta-analysis of 21 pain studies

- Data: 21 studies of pain in healthy subjects
- Results
  - GLM methods similar
  - Z-based methods similar
    - But FFX Z methods more sensitive (as expected)

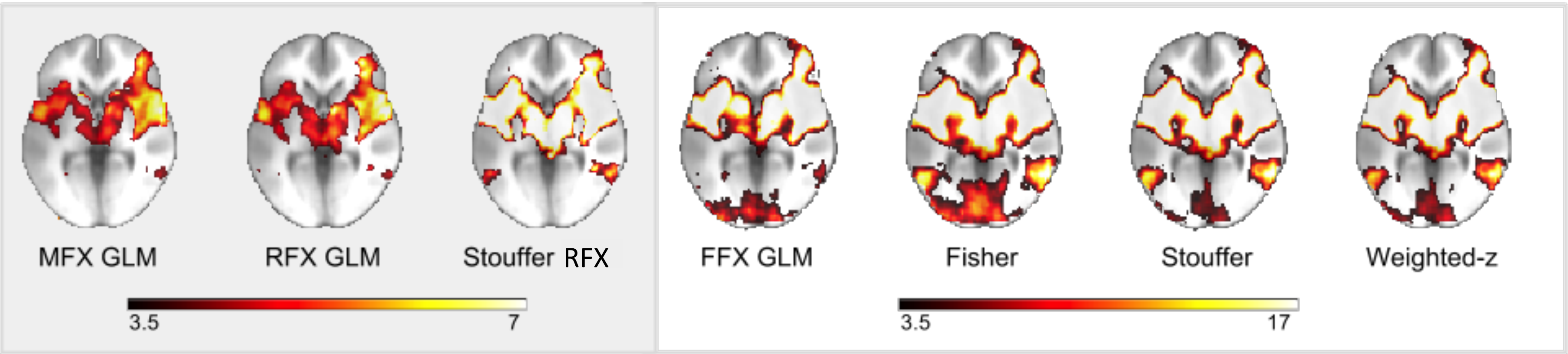


Fig. 1: Result of a meta-analysis of 21 pain studies for 4 fixed-effects (FFX GLM, Fisher, Stouffer, weighted-z) and 2 random-effects (RFX GLM, Stouffer MFX) meta-analytic approaches compared to the reference (MFX GLM) at a threshold of p<0.05 FDR corrected.

Data: Tracey pain group, FMRIB, Oxford.

Validity of IBMA approaches in neuroimaging

Simulations - Methods

- Simulated contrast estimates Y_i and Standard error S_i such as:

$$Y_i \sim \mathcal{N}(0, \frac{\sigma_i^2}{n_i} + \tau^2)$$

$$S_i^2 \sim \frac{\sigma_i^2}{n_i - 1}\chi^2_{(n_i-1)}$$

» Where

» Within-study variance

$$\sigma_i^2 \in [1/2, 1, 2, 4]$$

» Between-study variance

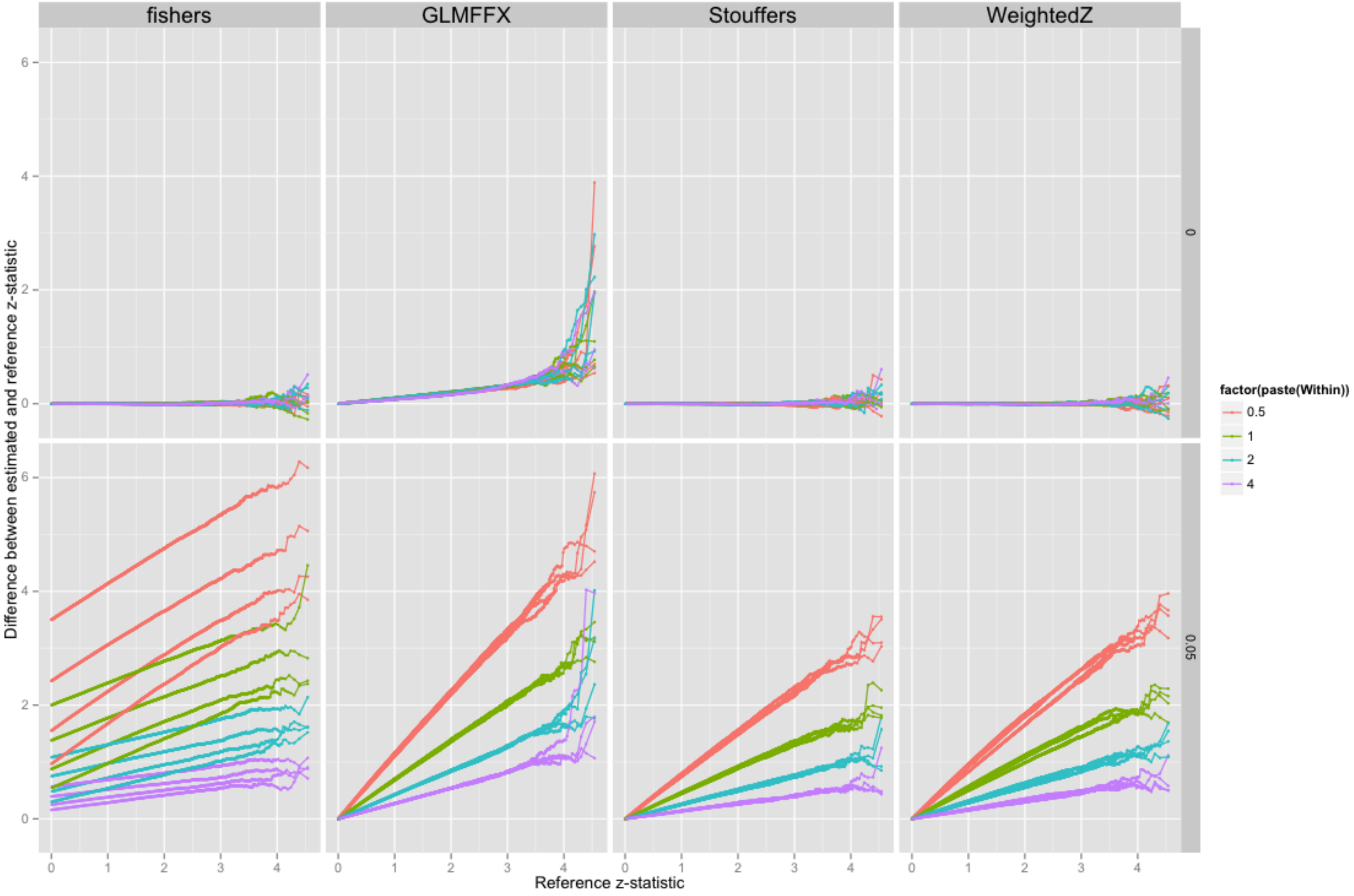
$$\tau^2 \in [0, 1/20]$$

» Sample size n_i

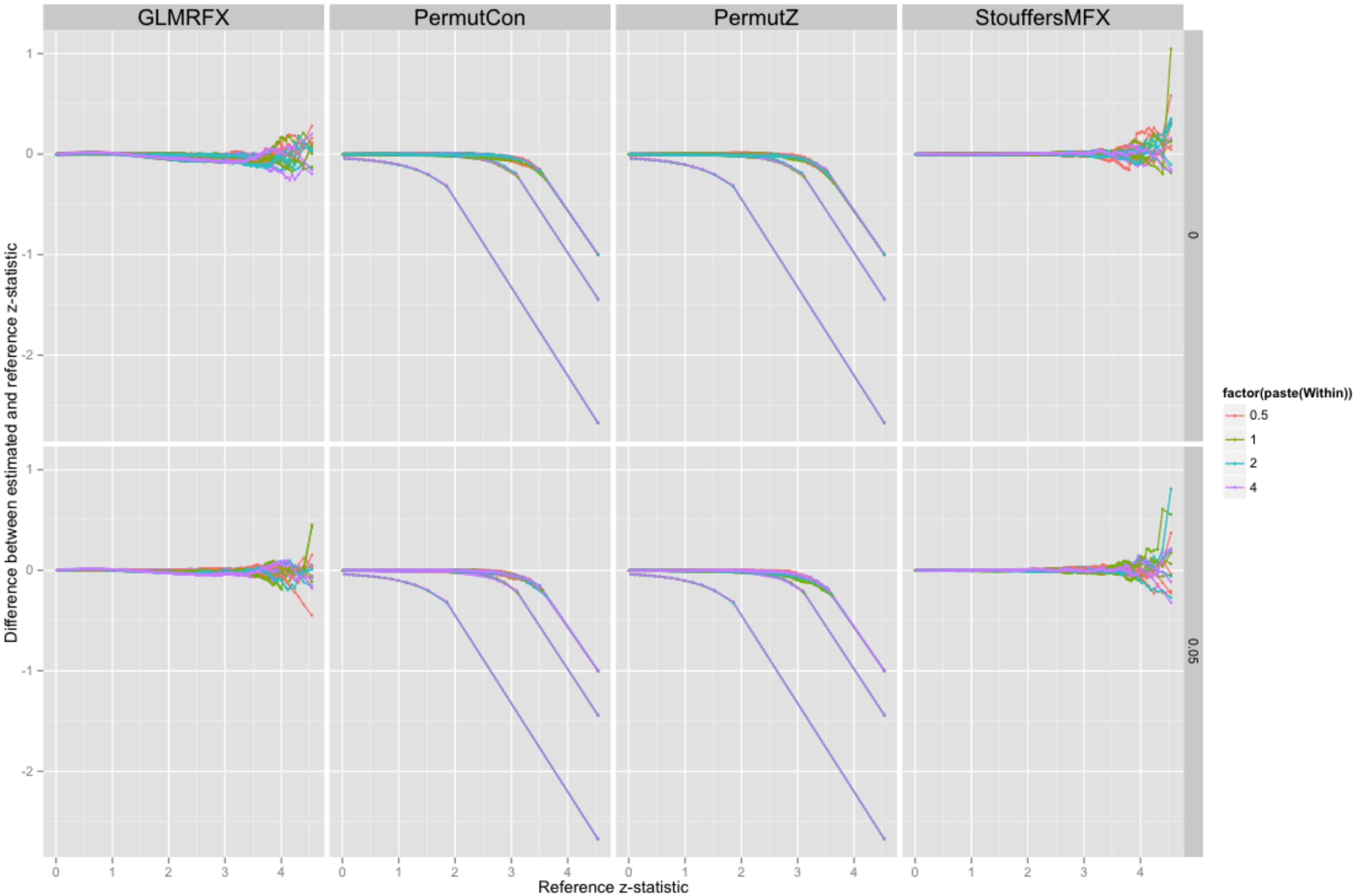
25% $\mathcal{U}(11, 20)$ ~50% $\mathcal{U}(21, 25)$

25% $\mathcal{U}(26, 50)$

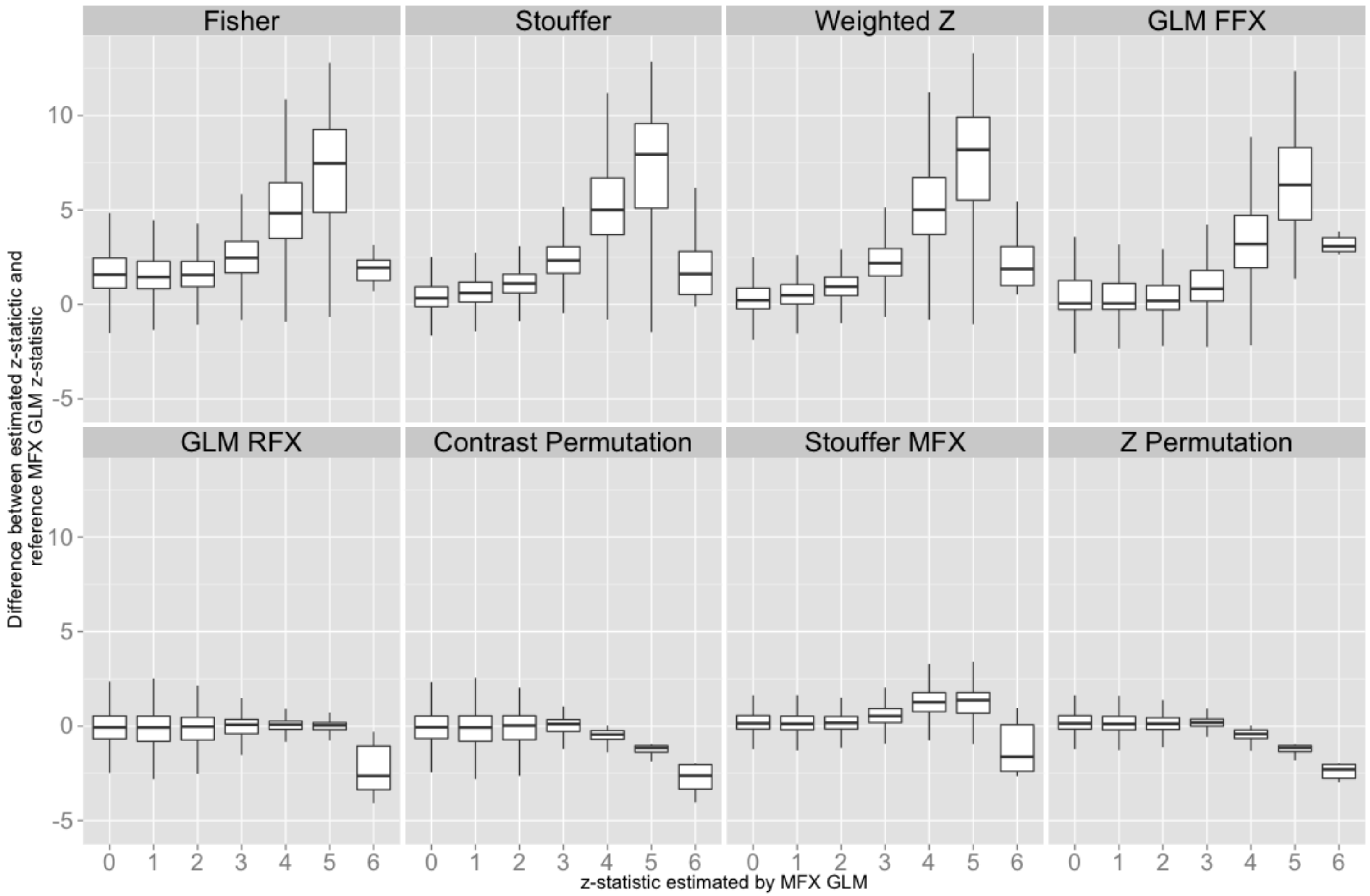
Simulations – Results (Fixed-Effects)



Simulations – Results (Random-Effects)



Meta-analysis of 21 pain studies



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Conclusions

- When data available, **Image-Based** preferred to **Coordinate-Based** meta-analysis
- **In practice**, it is **difficult** to use the gold standard **Mixed-Effects GLM**
  - Due to units issues, basically need FEAT for all 3 levels
- When only contrast estimates are available, **RFX GLM** is a practical & valid approach
- Few tools for Z-based IMBA, but underway…

For more on dealing with IBMA units problems…
Camille Maumet & Thomas Nichols, Poster 4036-W
"Do the units matter? Validity of Intensity Based Meta-Analysis in the presence of unit mismatches"

Thank you!

This work is supported by the wellcome trust

	Meta-analysis statistic	Nominal H_0 distribution	Inputs
FFX GLM	$\left(\sum_{i=1}^{k} \frac{Y_i}{S_i^2}\right) / \sqrt{\sum_{i=1}^{k} 1/S_i^2}$	$\mathcal{T}_{(\sum_{i=1}^{k} n_i - 1) - 1}$	Y_i, S_i^2
MFX GLM	$\left(\sum_{i=1}^{k} \frac{Y_i}{S_i^2 + \hat{\tau}^2}\right) / \sqrt{\sum_{i=1}^{k} 1/(S_i^2 + \hat{\tau}^2)}$	$\mathcal{T}_{k-1}$	Y_i, S_i^2
RFX GLM	$\left(\sum_{i=1}^{k} \frac{Y_i}{\sqrt{k}}\right) / \widehat{\sigma}_C^2$	$\mathcal{T}_{k-1}$	Y_i
Contrast Permutation	$\left(\sum_{i=1}^{k} \frac{Y_i}{\sqrt{k}}\right) / \widehat{\sigma}_C^2$	Empirical	Y_i
Fisher's	$-2 \sum_{i=1}^{k} \ln(\Phi(-Z_i)))$	$\chi^2_{(2k)}$	Z_i
Stouffer's	$\left(\sum_{i=1}^{k} Z_i\right) / \sqrt{k}$	$\mathcal{N}(0,1)$	Z_i
Weighted Stouffer's	$\left(\sum_{i=1}^{k} \sqrt{n_i} Z_i\right) / \sqrt{\sum_{i=1}^{k} n_i}$	$\mathcal{N}(0,1)$	Z_i, n_i
Z MFX	$\left(\sum_{i=1}^{k} Z_i\right) / \sqrt{k}\hat{\sigma}$	$\mathcal{T}_{k-1}$	Z_i
Z Permutation	$\left(\sum_{i=1}^{k} Z_i\right) / \sqrt{k}$	Empirical	Z_i

Table 1. Statistics for one-sample meta-analysis tests and their sampling distributions under the null hypothesis H_0. Empirical null distributions are determined using permutations with sign flipping.