

FMRI Data Analysis

Experiment Design

Scanning

Pre-Processing

Individual Subject Analysis: 1st level

Group Analysis: 2nd level

Post-Processing: clusterizing, ROI analysis, connectivity, ...

• Overview

- ☞ Why do we need to do group analysis?
- ☞ Fixed-effects analysis
- ☞ Mixed-effects analysis
 - ↳ Nonparametric approach
 - 3dWilcoxon, 3dMannWhitney, 3dKruskalWallis, 3dFriedman
 - ↳ Parametric approach
- ☞ Traditional parametric analysis
 - ↳ Effect size only: linear combination of regression coefficients (β)
 - 3dttest, 3dANOVA/2/3, 3dRegAna, GroupAna, 3dLME
- ☞ New group analysis method
 - ↳ Both effect size and precision: mixed-effects meta analysis (MEMA)
 - 3dMEMA

• Group Analysis: Fixed-Effects Analysis

☞ Number of subjects $n < 6$

☞ Case study: difficult to generalize to whole population

☞ Simple approach (**3dcalc**)

$$\triangleright t = \sum t_{ii} / \sqrt{n}$$

☞ Sophisticated approach

↳ Fixed-effects **meta** analysis (**3dcalc**): weighted least squares

$$\triangleright \beta = \sum w_i \beta_i / \sum w_i$$

$$\triangleright t = \beta \sum w_i / \sqrt{n}, w_i = t_i / \beta_i = \text{weight for } i\text{th subject}$$

↳ Direct fixed-effects analysis (**3dDeconvolve/3dREMLfit**)

↳ Combine data from all subjects and then run regression

• Group Analysis: Mixed-Effects Analysis

☞ Non-parametric approach

- $4 < \text{number of subjects} < 10$
- No assumption of data distribution (e.g., normality)
- Statistics based on ranking
- Individual and group analyses: separate

☞ Parametric approach

- Number of subjects ≥ 10
- Random effects of subjects: usually Gaussian distribution
- Individual and group analyses: separate

• Mixed-Effects: Non-Parametric Analysis

☞ Programs: roughly equivalent to permutation tests

➤ **3dWilcoxon** (~ paired t -test)

➤ **3dFriedman** (~ one-way within-subject with **3dANOVA2**)

➤ **3dMannWhitney** (~ two-sample t -test)

➤ **3dKruskalWallis** (~ between-subjects with **3dANOVA**)

☞ Pros: Less sensitive to outliers (more robust)

☞ Cons

➤ Multiple testing correction **limited** to FDR (**3dFDR**)

➤ Less flexible than parametric tests

○ Can't handle complicated designs with more than one fixed factor

○ Can't handle covariates

- **Mixed-Effects: Basic concepts in parametric approach**

- **Fixed factor/effect**

- ↳ Treated as a **fixed** variable (constant) in the model
 - Categorization of experiment conditions/tasks (modality: visual/audial)
 - Group of subjects (gender, normal/patients)
- ↳ All **levels** of the factor are of interest
- ↳ Fixed in the sense statistical inferences
 - apply only to the specific levels of the factor
 - don't extend to other potential levels that might have been included

- **Random factor/effect**

- ↳ Treated as a **random** variable in the model: exclusively **subject** in FMRI
 - average + effects uniquely attributable to each subject: *e.g.* $N(\mu, \sigma^2)$
- ↳ Each individual subject is of NO interest
- ↳ Random in the sense
 - subjects serve as a random sample (representation) from a population
 - inferences can be generalized to a **hypothetical** population

- **Mixed-Effects**: In case you love equations too much!!!

- ↳ Linear model

- ↳ $Y = X\beta + \varepsilon, \varepsilon \sim N_n(0, \sigma^2 I_n)$

- ↳ Only one random effect, residual ε

- ↳ Individual subject analysis in FMRI

- ↳ Linear mixed-effects (LME) model

- ↳ $Y = X\beta + Zb + \varepsilon, b \sim N(0, \psi), \varepsilon \sim N(0, \Lambda)$

- ↳ Two random effect components: cross-subject effect Zb and within-subject effect ε

- ↳ Group analysis in FMRI: t -tests and ANOVAs are special cases of LME with idealized assumptions

• Mixed-Effects: Mixed-Effects Analysis

👉 Programs

- **3dttest** (one-sample, two-sample and paired t)
- **3dANOVA** (one-way between-subject)
- **3dANOVA2** (one-way within-subject, 2-way between-subjects)
- **3dANOVA3** (2-way within-subject and mixed, 3-way between-subjects)
- **3dRegAna** (regression/correlation, plus covariates)
- **GroupAna** (Matlab package for up to 5-way ANOVA)
- **3dLME** (R package for all sorts of group analysis)
- **3dMEMA** (R package for meta analysis, t-tests plus covariates)

• Mixed-Effects: Which program should I use?

☞ Two perspectives: batch vs. piecemeal

➤ Experiment design

➤ Factors/levels, balancedness

* ANOVA: main effects, interactions, simple effects, contrasts, ...

* Linear mixed-effects model

➤ Most people are educated in this traditional paradigm!

➤ Pros: get almost everything you want in one batch model

➤ Cons: F -stat for main effect and interaction is difficult to comprehend sometimes: a condensed/summarized test with vague information when levels/factors greater than 2
(**I don't like F -test personally!!! Sorry, Ronald A. Fisher...**)

➤ Tests of interest

➤ Simple and straightforward: Focus on each individual test, attack one at a time!

➤ Mainly t -stat: one-sample, paired, two-sample

➤ All main effects and interactions can be broken into multiple t -tests

• Jack of All Trades (well, almost): `3dtttest`

☞ Basic usage

↪ One-sample t

- One group: simple effect; Example: 10 subjects under condition $Vrel$ with $H_0: \mu_V = 0$

↪ Two-sample t

- Two groups: Compare one group with another
- ~ 1-way between-subject (`3dANOVA2 -type 1`)
- Unequal sample sizes allowed
- Homoskedasticity vs. heteroskedasticity: **-unpooled**
- Example: 15 TD subjects vs. 13 autism subjects - $H_0: \mu_A = \mu_B$

↪ Paired t

- Two conditions of one group: Compare one condition with another
- ~ one-way within-subject (`3dANOVA2 -type 3`)
- ~ one-sample t on individual contrasts
- Example: Difference of visual and auditory conditions for 10 subjects with $H_0: \mu_V = \mu_A$

☞ Output: 2 values (effect and t)

☞ Versatile program: **Most tests can be done with `3dtttest`** - piecemeal vs. bundled

☞ **-mask** option unavailable but desirable!

• 3dtttest: Example

- Paired t-test

```
3dtttest -prefix ttest_V-A -paired \  
  -set1 \  
    'OLSQ.FP.betas+tlrc[1]' \  
    'OLSQ.FR.betas+tlrc[1]' \  
    ..... \  
    'OLSQ.GM.betas+tlrc[1]' \  
  -set2 \  
    'OLSQ.FP.betas+tlrc[0]' \  
    'OLSQ.FR.betas+tlrc[0]' \  
    ..... \  
    'OLSQ.GM.betas+tlrc[0]'
```

} Model type,

} Input files for Arel condition

} Input files for Vrel condition

- ANOVA program 1 : 3dANOVA

- ↳ Generalization of two-sample *t*-test

- ↳ One-way between-subject: 2 or more groups of subjects
- ↳ H_0 : no difference across all levels (groups)
- ↳ Examples of groups: gender, age, genotype, disease, *etc.*
- ↳ Unequal sample sizes allowed

- ↳ Assumptions

- ↳ Normally distributed with **equal variance** across groups

- ↳ Results: 2 values (% and *t*)

- ↳ **3dANOVA vs. 3dttest**

- ↳ Equivalent with 2 levels (groups) if equal variance is assumed
- ↳ More than 2 levels (groups): Can run multiple two-sample *t*-test
- ↳ 3dttest allows **heteroscedasticity** (unequal variance across groups)

- ANOVA program 2: 3dANOVA2

- ↳ Designs: **generalization of paired t -test**

- ↳ One-way within-subject (**type 3**)

- ↳ Major usage

- ↳ Compare conditions in one group

- ↳ Extension and equivalence of paired t

- ↳ Two-way between-subjects (**type 1**)

- ↳ 1 condition, 2 classifications of subjects

- ↳ Extension and equivalence two-sample t

- ↳ Unbalanced designs disallowed: Equal number of subjects across groups

- ↳ Output

- ↳ Main effect (**-fa**): F

- ↳ Interaction for two-way between-subjects (**-fab**): F

- ↳ Contrast testing

- ↳ Simple effect (**-amean**)

- ↳ 1st level (**-acontr**, **-adiff**): among factor levels

- ↳ 2nd level (interaction) for two-way between-subjects

- ↳ 2 values per contrast: % and t

• 3dANOVA2: Example

- Two factors: A – condition (fixed, 2 levels); B – subject (random, 10 levels).
- Script s1.3dANOVA2 under ~/AFNI_data6/group_results/

```
3dANOVA2 -type 3 -alevels 2 -blevels 10
```

```
-mask mask+tlrc
```

```
-dset 1 1 'OLSQ.FP.betas+tlrc[Vrel#0_Coef]'
```

```
-dset 2 1 'OLSQ.FP.betas+tlrc[Arel#0_Coef]'
```

```
-dset 1 2 'OLSQ.FR.betas+tlrc[Vrel#0_Coef]'
```

```
-dset 2 2 'OLSQ.FR.betas+tlrc[Arel#0_Coef]'
```

```
.....
```

```
-dset 1 10 'OLSQ.GM.betas+tlrc[Vrel#0_Coef]'
```

```
-dset 2 10 'OLSQ.GM.betas+tlrc[Arel#0_Coef]'
```

```
-amean 1 V
```

```
-amean 2 A
```

```
-adiff 1 2 VvsA
```

```
-fa FullEffect
```

```
-bucket anova.VA
```

\ } Model type,
\ } Factor levels

\ } Input for each cell in
\ } ANOVA table:
\ } Totally 2X10 = 20

\ } *t* tests: one-sample type

\ } *t* test: two-paired

\ } *F* test: main effect

\ } Output: bundled

All the F/t-tests here can be obtained with 3dttest!

• ANOVA program 3 : 3dANOVA3

☞ Designs

↳ **Two-way within-subject (type 4)**: Crossed design AXBXC

➤ Generalization of paired *t*-test

➤ One group of subjects

➤ Two categorizations of conditions: A and B

↳ **Two-way mixed (type 5)**: Nested design BXC(A)

➤ Two or more groups of subjects (Factor A): subject classification, e.g., gender

➤ One category of condition (Factor B)

➤ Nesting: balanced

↳ **Three-way between-subjects (type 1)**

➤ 3 categorizations of groups

☞ Output

↳ Main effect (**-fa** and **-fb**) and interaction (**-fab**): *F*

↳ Contrast testing

➤ 1st level: **-amean**, **-adiff**, **-acontr**, **-bmean**, **-bdiff**, **-bcontr**

➤ 2nd level: **-abmean**, **-aBdiff**, **-aBcontr**, **-Abdiff**, **-Abcontr**

➤ 2 values per contrast : % and *t*

- ANOVA program 4: GroupAna

- ↳ Pros

- ↳ Matlab script package for up to 5-way ANOVA
- ↳ Can handle both volume and surface data
- ↳ Can handle following unbalanced designs (two-sample *t* type):
 - 3-way ANOVA type 3: BXC(A)
 - 4-way ANOVA type 3: BXCXD(A)
 - 4-way ANOVA type 4: CXD(AXB)

- ↳ Cons

- ↳ Use a commercial packag: requires Matlab plus Statistics Toolbox
- ↳ Difficult to test and interpret simple effects/contrasts
- ↳ Complicated design, and compromised power
- ↳ GLM approach (slow): heavy duty computation: minutes to hours
 - Input with lower resolution recommended
 - Resample with `adwarp -dxyz #` and `3dresample`

- ↳ See <http://afni.nimh.nih.gov/sscc/gangc> for more info

- **Regression: 3dRegAna**

- ☞ Correlation analysis

- ↳ Between brain response and some covariates

- ↳ Covariates are **subject-level** variables

- behavioral data

- physical attributes, e.g., age, IQ, brain volume, etc.

- ☞ **3dRegAna**

- ↳ One- or two-sample *t*-test + covariates

- ☞ See <http://afni.nimh.nih.gov/sscc/gangc/ANCOVA.html> for more info

• Linear Mixed-Effects Analysis: 3dLME

👉 Pros

- ↳ R package: open source platform
- ↳ Linear mixed-effects (LME) modeling
- ↳ Versatile: handles almost all situations in one package
 - Unbalanced designs (unequal number of subjects, missing data, etc.)
 - ANOVA and ANCOVA, but unlimited factors and covariates
 - **Able to handle HRF modeling with basis functions**
 - Violation of sphericity: heteroscedasticity, variance-covariance structure

👉 Cons

- ↳ High computation cost (lots of repetitive calculation)
- ↳ Controversial regarding degrees of freedom

👉 See <http://afni.nimh.nih.gov/sscc/gangc/lme.html> for more information

• Linear Mixed-Effects Analysis: 3dLME

☞ Running LME: HRF modeled with 6 tents

↳ Null hypothesis $H_0: \beta_1 = \beta_2 = \dots = \beta_6 = 0$ (NOT $\beta_1 = \beta_2 = \dots = \beta_6$)

```
Data:Volume                <-- either Volume or Surface
Output:test                <-- any string (no suffix needed)
MASK:Mask+tlrc.BRIK       <-- mask dataset
FixEff:Time-1              <-- model formula for fixed effects
COV:                       <-- covariate list
RanEff: 1                  <-- random effect specification
VarStr:weights=varIdent(form=~1|Time) <-- heteroscedasticity?
CorStr:correlation=corAR1(form=~Order|Subj) <-- correlation structure
SS:sequential              <-- sequential or marginal
Clusters:4
Subj      Time      TimeOrder  InputFile
Jim       t1         1      contrastT1+tlrc.BRIK
Jim       t2         2      contrastT2+tlrc.BRIK
.....
Jim       t6         6      contrastT6+tlrc.BRIK
```

Mixed-Effects Meta Analysis: 3dMEMA

■ Requirements

- ❑ R installment, plus ‘snow’ package for parallel computing

■ 3 running modes

- ❑ **Scripting**: type ‘3dMEMA –help’ at terminal to see usage
- ❑ **Sequential/interactive** mode inside R: `source("~/abin/3dMEMA.R")`
- ❑ **Batch** (if answers known): `R CMD BATCH Cmds.R myDiary &`

■ Pros

- ❑ Makes more sense: better statistical properties
- ❑ Likely more statistically powerful
- ❑ Less prone to outliers
- ❑ Provides more diagnostic measures
- ❑ Can include covariates in the analysis

■ Cons

- ❑ Longer runtime
 - ❑ Can’t handle sophisticated situations: basis functions, ANOVAs, ...
-

3dMEMA: example-scripting

Paired type test: visual-reliable vs. auditory-reliable (script [s4.3dMEMA.V-A](#) under AFNI_data6/group_results/)

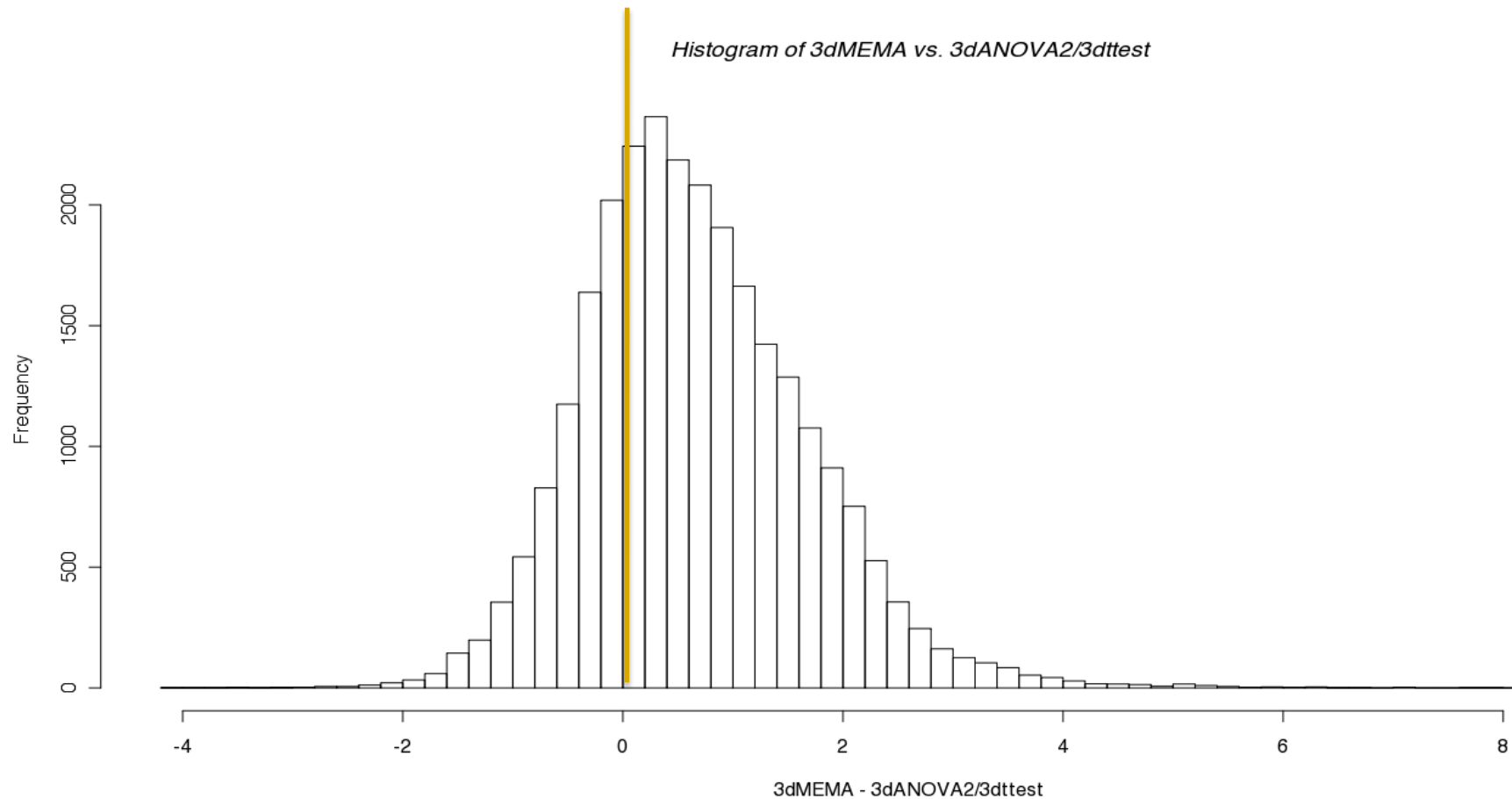
```
3dMEMA -prefix mema_V-A -mask mask+tlrc -jobs 4 -max_zeros 3 \
  -conditions Vrel Arel -Hktest -model_outliers \
  -set Arel \
    FP 'REML.FP.bt+tlrc[2]' 'REML.FP.bt+tlrc[3]' \
    FR 'REML.FR.bt+tlrc[2]' 'REML.FR.bt+tlrc[3]' \
    .... \
    GK 'REML.GK.bt+tlrc[2]' 'REML.GK.bt+tlrc[3]' \
    GM 'REML.GM.bt+tlrc[2]' 'REML.GM.bt+tlrc[3]' \
  -set Vrel \
    FP 'REML.FP.bt+tlrc[0]' 'REML.FP.bt+tlrc[1]' \
    FR 'REML.FR.bt+tlrc[0]' 'REML.FR.bt+tlrc[1]' \
    .... \
    GK 'REML.GK.bt+tlrc[0]' 'REML.GK.bt+tlrc[1]' \
    GM 'REML.GM.bt+tlrc[0]' 'REML.GM.bt+tlrc[1]'
```

3dMEMA: example-interactive/batch

- One-sample test: visual-reliable
 - Sequential/interactive mode on R prompt
 - Demo here
 - Batch mode: `R CMD BATCH scriptCMD.R myDiary.txt &`
 - Remote running: `nohup R CMD BATCH scriptCMD.R myDiary.txt &`
-

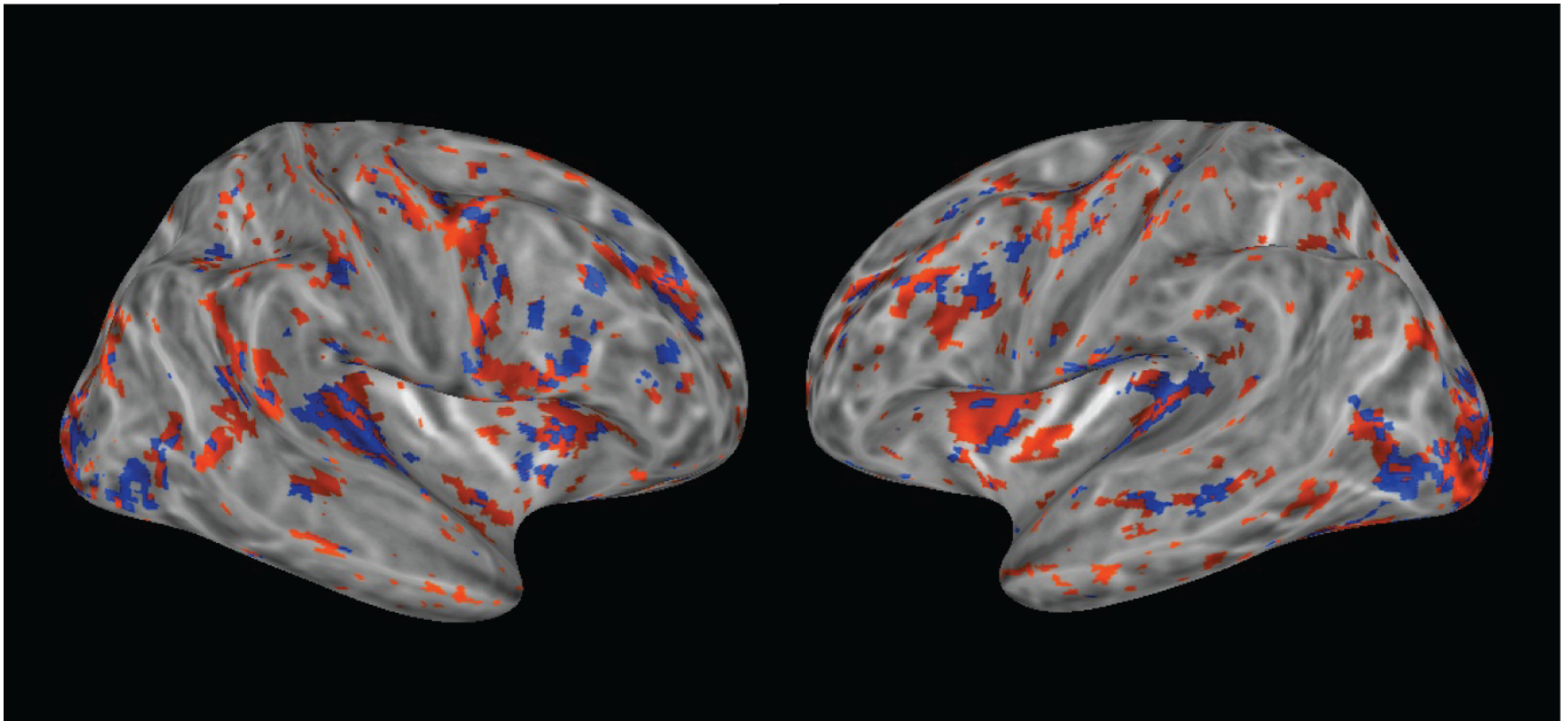
3dMEMA: comparison with 3dttest

- Majority of significant voxels with 3dMEMA gained power with a threshold of 2.0 for $t(30)$



3dMEMA: comparison with 3dttest

- Majority of significant voxels with 3dMEMA gained power (**red**: 3dMEMA higher; **blue**: 3dttest higher) with a threshold of 2.0 for $t(9)$.



Why new group analysis approach?

- Our ultimate goal is not just to gain statistical power
 - Old group analysis approach
 - Take β 's from each subject, and run t -test, AN(C)OVA, LME
 - Three assumptions
 - Within/intra-subject variability (standard error, sampling error) is relatively small compared to cross/between/inter-subjects variability
 - Within/intra-subject variability roughly the same across subjects
 - Normal distribution for cross-subject variability (**no outliers**)
 - Violations seem everywhere: violating either can lead to suboptimal/invalid analysis
 - Common to see 40% up to 100% variability due to within-subject variability
 - Non-uniform within/intra-subject variability across subjects
-

How can we do it differently?

- For each effect estimate (β or linear combination of β 's)
 - Information regarding our confidence about the effect?
 - Reliability/precision/efficiency/certainty/confidence: standard error (SE)!
 - Smaller SE \rightarrow higher reliability/precision/efficiency/certainty/confidence
 - SE of an effect = estimated standard deviation (SD) of the effect
 - t -statistic of the effect
 - Signal-to-noise or effect vs. uncertainty: $t = \beta/SE$
 - SE contained in t -statistic: $SE = \beta/t$
 - Trust those β 's with high reliability/precision (small SE) through weighting/compromise
 - β estimate with high precision (lower SE) has more say in the final result
 - β estimate with high uncertainty gets downgraded
-

Differentiate effects based on precision

■ Dealing with outliers

- Unreliable estimate (small t): small/big β + big SE
 - Will automatically be downgraded
 - May still slightly bias cross-subjects variability estimate to some extent, leading to unfavorable significance testing, but much better than conventional approach
 - Reliable estimate (big t): small/big β + small SE
 - Weighting only helps to some extent: if one subject has extremely small SE (big t), the group effect may be dominated by this subject
 - Needs delicate solutions: fundamentally why outliers?
 - Brain level: Considering covariate(s)? Grouping subjects?
 - Singular voxels: special modeling on cross-subject variance
-

Running 3dMEMA

- Currently available analysis types (+ covariates allowed)
 - **One-sample**: one condition with one group
 - **Two-sample**: one condition across 2 groups with homoskedasticity (same variability)
 - **Paired-sample**: two conditions with one group
 - **Two-sample**: one condition across 2 groups with heteroskedasticity (different variability)
 - Output
 - Group level: % signal change + Z/t-statistic, $\tau^2 + Q$
 - Individual level: $\lambda + Z$ for each subject
 - Modes
 - Scripting
 - Sequential mode on terminal
 - Batch mode: `R CMD BATCH cmds.R diary.txt &`
-

3dMEMA limitations

- Basis functions?
 - Stick with 3dLME for now
 - ANOVA?
 - Extension difficult
 - t -tests should be no problem
 - F -tests?
 - Some of them boil down to t -tests, for example: F -test for interaction between A and B (both with 2 levels) with “3dANOVA3 -type 5...”: equivalent to t -test for $(A1B1-A1B2)-(A2B1-A2B2)$ or $(A1B1-A2B1)-(A1B2-A2B2)$, but we can say more with t than F : a positive t shows $A1B1-A1B2 > A2B1-A2B2$ and $A1B1-A2B1 > A1B2-A2B2$
 - Do something for other F in the future?
-

Covariates

□ Covariates

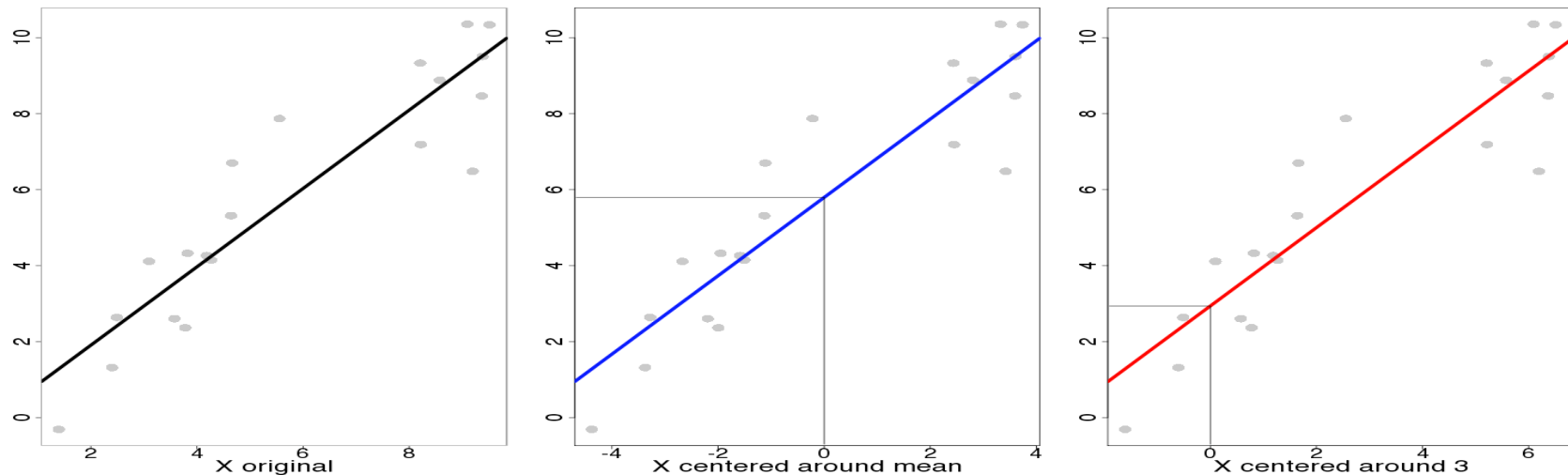
- May or may not be of direct interest
- Confounding, nuisance, or interacting variables
- **Subject-level** (vs. trial-level: handled via amplitude modulation)
- Controlling for variability in the covariate
- Continuous or discrete?
- One-sample model $y_i = \alpha_0 + \alpha_1 x_i + \delta_i + \varepsilon_i$, for i th subject
- Two-sample model $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + \varepsilon_i$

□ Examples

- Age, IQ, brain volume, cortex thickness
 - Behavioral data
-

Handling covariates: one group

- ❑ Centering: tricky business (using **age** as an example)
 - ❑ $y_i = \alpha_0 + \alpha_1 x_i + \delta_i + \varepsilon$, for i th subject
 - ❑ Interested in group effect α_0 ($x=0$) while controlling (partialling out) x
 - ❑ α_1 - slope (change rate): % signal change per unit of x
 - ❑ Interpretability: group effect α_0 at what value of x : mean or any other value?



Covariates: trickier with 2 groups

□ Center and slope

□ $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + \varepsilon$, for i th subject

■ x_1 : group indicator

■ x_2 : covariate

■ x_3 : group effect in slope (interaction btw group and covariate)

□ What we're interested

■ Group effects α_0 and α_1 while controlling covariate

□ Interpretability

■ Center

□ Group effect α_0 and α_1 at what covariate value?

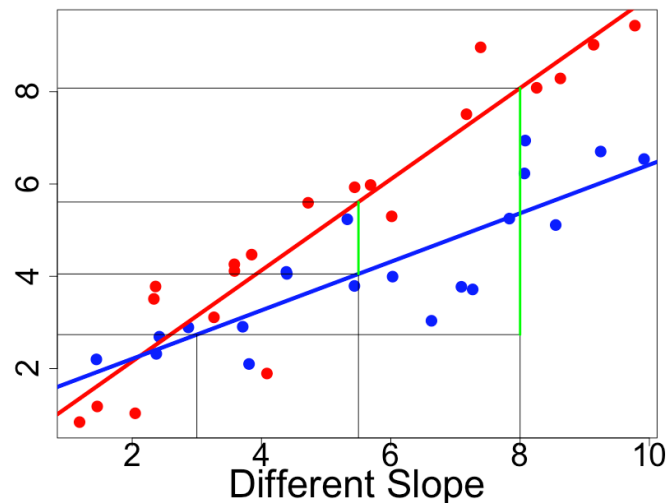
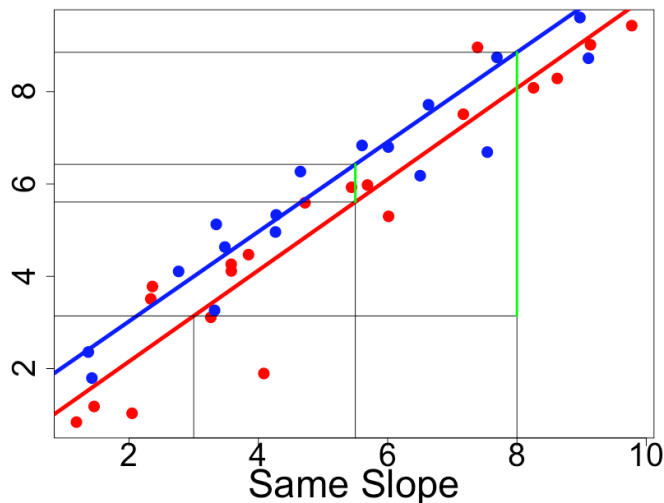
□ Same or different center across groups?

■ Slope

□ same ($\alpha_3=0$) or different ($\alpha_3 \neq 0$) slope across groups

Covariates: scenarios with 2 groups

- Center and slope (again using [age](#) as an example)
 - $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + \varepsilon_i$ for i th subject
 - Interpretability
 - Same center and slope ($\alpha_3=0$)
 - Different center with same slope ($\alpha_3=0$)
 - Same center with different slope ($\alpha_3 \neq 0$)
 - Different center and slope ($\alpha_3 \neq 0$)



Start simple: one-sample test

- Random-effects: $y_i = \theta_i + \varepsilon_i = \alpha_0 + \delta_i + \varepsilon_i$, for i th subject
 - y_i : β or linear combination (contrast) of β 's from i th subject
 - $\theta_i = \alpha_0 + \delta_i$: “true” individual effect from i th subject
 - α_0 : group effect we'd like to find out
 - δ_i : deviation of i th subject from group effect α_0 , $N(0, \tau^2)$
 - ε_i : sample error from i th subject, $N(0, \sigma_i^2)$, σ_i^2 known!
- Special cases
 - $\sigma_i^2 = 0$ reduced to conventional group analysis: One-sample t : $y_i = \alpha_0 + \delta_i$
 - $\delta_i = 0$ ($\tau^2 = 0$) assumed in fixed-effects (FE) model: Ideally we could find out all possible explanatory variables so only an FE model is necessary!
- Mature meta analysis tools for this simple model
 - Broadly used in clinical trials/epidemiology in recent 20 yrs
 - A special case of linear mixed-effects model

MEMA with one-sample test

- **Random-effects:** $y_i = \alpha_0 + \delta_i + \varepsilon_i$, for i th subject
 - $\delta_i \sim N(0, \tau^2)$, $\varepsilon_i \sim N(0, \sigma_i^2)$, σ_i^2 known, τ^2 unknown
 - What can we achieve?
 - Null hypothesis about group effect $H_0: \alpha_0 = 0$
 - Checking group heterogeneity $H_0: \tau^2 = 0$
 - Any outliers among the subjects? Adding some confounding variable(s)?
Grouping subjects?
 - We know σ_i^2 , and pretend we also **knew** τ^2 , weighted least squares (WLS) gives
 - The “**best**” estimate $\hat{\alpha}_0 = \frac{\sum w_i y_i}{\sum w_i}$, $w_i = \frac{1}{\tau^2 + \sigma_i^2}$
 - **BLUE**: unbiased with minimum variance
 - Wake up: Unfortunately we don't know τ^2 !!!

Solving MEMA in one-sample case

- Estimating τ^2 : a few approaches
 - Method of moment (MoM) - DSL
 - Maximum likelihood (ML)
 - Restricted/residual/reduced/marginal ML (REML): 3dMEMA
- Statistical testing
 - Group effect $\alpha_0=0$: $Z = \frac{\sum w_i y_i}{\sqrt{\sum w_i}} \cong N(0,1), w_i = \frac{1}{\tau^2 + \sigma_i^2}$
 - Wald or Z-test: assume enough subjects with normal distributions
 - Go with t -test when in doubt
 - Heterogeneity test $\tau^2=0$: $Q = \sum_{i=1}^n \frac{(y_i - \hat{\alpha}_0)^2}{\sigma_i^2} \sim \chi^2(n-1)$
 - Outlier identification for each subject through Z-statistic

We don't limit ourselves to simple case

- $y_i = \alpha_0 + \alpha_1 x_{i1} + \dots + \alpha_{ip} x_{ip} + \delta_i + \varepsilon_i$ for i th subject
 - Mixed-effects model or meta regression
 - y_i : β or linear combination (contrast) of β 's from i th subject
 - α_0 : common group effect we'd like to find out
 - x_{ij} : an indicator/dummy variable showing, for example, group to which i th subject belongs, level at which a factor lies, or a continuous variable such as covariate (e.g., age, IQ) ($j=1, \dots, p$)
 - δ_i : deviation of i th subject from group effect α_0 , $N(0, \tau^2)$
 - ε_i : sample error from i th subject, $N(0, \sigma_i^2)$, σ_i^2 known!
- Combine subjects into a concise model in matrix form
 - $\mathbf{y}_{n \times 1} = \mathbf{X}_{n \times p} \boldsymbol{\alpha}_{p \times 1} + \boldsymbol{\delta}_{n \times 1} + \boldsymbol{\varepsilon}_{n \times 1}$
 - $\mathbf{y} \sim N(\mathbf{X}\boldsymbol{\alpha}, \tau^2 \mathbf{I}_n + \mathbf{V})$, $\mathbf{V} = \text{diag}(\sigma_1, \dots, \sigma_n)$ known, τ^2 unknown
 - Estimate $\boldsymbol{\alpha}$ and τ^2 simultaneously via maximizing REML

Dealing with outliers

□ Detection

- Ideally we wish to account for anything until having no cross-subject variability: $\tau^2 = 0$!
- 4 quantities to check cross-subject variability
 - Cross subject variability (heterogeneity) τ^2
 - Q for $H_0: \tau^2 = 0$
 - Intra-class correlation (ICC): $\lambda = \sigma_i^2 / (\sigma_i^2 + \tau^2)$
 - Z statistic of ε_i

□ Modeling: how to handle outliers in the model?

- Ignore those subjects with 2 s.d. away from mean?
 - Arbitrary: OK with data within 1.9 s.d.?
 - How about when outliers occur at voxel level?
 - If throwing away outliers at voxel level, varying DFs across brain?
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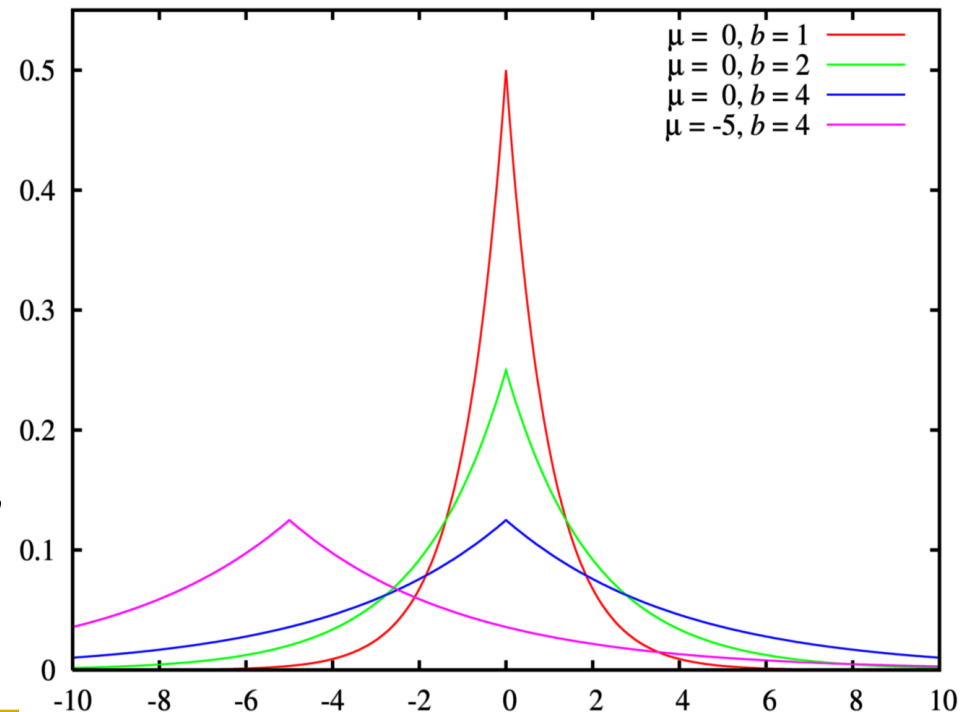
Modeling outliers

- Modeling: how to handle outliers in the model?
 - Typically a Gaussian for subject deviation: $\delta_i \sim N(0, \tau^2)$
 - With outliers, assume a Laplace (double exponential) distribution

$$f(x|\mu, b) = \frac{1}{2b} \exp\left(-\frac{|x - \mu|}{b}\right)$$

- μ : location parameter
- b : scale parameter
- Mean=median=mode= μ
- Variance = $2b^2$
- Fatter tail but smaller Var
- Estimator of μ is sample median, and ML estimator of b

$$\hat{b} = \frac{1}{N} \sum_{i=1}^N |x_i - \hat{\mu}|$$



Modeling outliers

- ❑ Laplace distribution for outlier modeling
 - ❑ No REML form
 - ❑ Go with ML: variance estimate τ^2 might be slightly underestimated
 - ❑ Computation cost: higher
 - ❑ Generally higher statistical power
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Moral of a story

■ Story

- Strong activation at individual level and in ROI analysis failed to show up at group level
- Result with 3dMEMA showed consistency with individual and ROI analysis
- Magic power of 3dMEMA? Relatively robust to some (unreliable) outliers

■ Check brick labels for all input files

```
foreach subj (S1 S2 S3 ...)  
  3dinfo -verb ${subj}_file+tlrc | grep 'sub-brick #0'  
end
```

```
++ 3dinfo: AFNI version=AFNI_2008_07_18_1710 (Jul 8 2009) [32-bit]  
-- At sub-brick #0 'contr_GLT#0_Coef' datum type is float:  -0.78438 to  0.867817  
-- At sub-brick #0 'contr_GLT#0_Coef' datum type is float:  -0.444093 to  0.501589  
...
```

Suggested preprocessing steps

- ❑ Input
 - ❑ β and t -statistic from each subject
 - ❑ One sub-brick per input file (3dbucket)
 - ❑ Some suggestions
 - ❑ Slice timing correction and volume registration
 - ❑ Aligning/warping to standard space
 - ❑ Avoid troubling step of warping on t -statistic
 - ❑ Smoothing: 3dBlurToFWHM
 - ❑ Scaling
 - ❑ All input files, β and more importantly t -statistic, come from 3dREMLfit instead of 3dDeconvolve
 - ❑ No masking applied at individual level so that no data is lost at group level along the edge of (and sometimes inside) the brain
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Comparisons among fMRI packages

Program	Language	Algorithm	Runtime	Group effect statistics	Covariates	Voxelwise outlier detection	Voxelwise outlier modeling
multistat (fMRIstat)	Matlab	EM for REML + spatial regularization	~1 min per test	t	✗	✗	✗
FLAME in FEAT (FSL)	C/C++	Bayesian + MCMC	45-200 min per test + threshold	fitted with t	✓	% subjects for group, p for each subject	mixture of two Gaussian
3dMEMA (AFNI)	R	ML/REML/MoM	3-15 min per test	Z/t	✓	$\tau^2 + Q$ for group, $\lambda + Z$ for each subject	Laplace

Overview: 3dMEMA

- ❑ <http://afni.nimh.nih.gov/sscc/gangc/MEMA.html>
 - ❑ Meta analysis: compromise between Bayesian and frequentist
 - ❑ Backbone: WLS + maximization of REML or ML of Laplace-Gauss
 - ❑ Currently available types
 - ❑ One-, two-, paired-sample test
 - ❑ Covariates allowed: careful with centering and interaction with groups
 - ❑ Output
 - ❑ Group level: group effect (% signal change) and statistics (Z/t), cross-subject heterogeneity τ^2 and Q (χ^2 -test)
 - ❑ Individual level: $\lambda + Z$ for each subject
 - ❑ Generally more powerful/valid than conventional approach
 - ❑ Relatively robust against most outliers
 - ❑ Moderate computation cost with parallel computing: 3-20 minutes
 - ❑ Limitations
 - ❑ Can't handle sophisticated types: multiple basis functions; F -test types
 - ❑ Computation cost
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