

Group Analysis

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Preview

- Concepts and terminology
- Group analysis approaches
 - GLM: 3dtttest++, 3dMEMA
 - GLM, ANOVA, ANCOVA: 3dMVM
 - LME: 3dLME, 3dLMER
 - Assumed vs. estimated HDR
- Miscellaneous
 - Issues with covariates
 - Intra-Class Correlation (ICC)
 - Inter-Subject Correlation (ISC)

Program List

- **3dtest++** (GLM: one-, two-sample, paired t , between-subjects variables)
- **3dMVM** (generic AN(C)OVA)
- **3dLME, 3dLMER** (sophisticated random-effects structure, missing data, within-subject covariates)
- **3dMEMA** (similar to 3dtest++: measurement errors)
- **3dICC** (intraclass correlation)
- **3dISC** (inter-subject correlation)
- **RBA** (region-based analysis)
- **MBA** (matrix-based analysis)
- **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)

Why Group Analysis?

- Reproducibility and generalization
 - Summarization
 - Generalization: from current results to population level
 - Sample size: typically 10 or more subjects per group
 - Individualized inferences: case studies, pre-surgical planning, lie detection, classifications, machine learning, ...

- One model combining both steps?
 - + Ideal: less information loss, more accurate inferences
 - - Historical
 - - Computationally unmanageable, and very hard to set up
 - - Data quality check at individual level
 - - Flexible group-level model

Simplest case

- BOLD responses from a group of 20 subjects
 - data: $(\beta_1, \beta_2, \dots, \beta_{20}) = (1.13, 0.87, \dots, 0.72)$
 - mean: 0.92
 - standard deviation: 0.40, 0.90
 - Do we have strong evidence for the effect?

- Modeling perspective

- Simple GLM: one-sample t -test

$$\hat{\beta}_i = b + \epsilon_i, \epsilon_i \sim N(0, \sigma^2)$$

- Statistical evidence - t -test
- Summary: b (dimensional), **SE**, and t / p (dimensionless)

Chen et al. (2017). Is the statistic value all we should care about in neuroimaging? Neuroimage 147:952-959.

Terminology

- Response/outcome variable: left-hand side of model
 - Regression β coefficients (plus measurement errors)
 - Structured: subjects, tasks, groups
- Explanatory variables: right-hand side of model
 - Categorical (factors) vs quantitative (covariates)
 - Fixed- vs random-effects: conventional statistics
- Models
 - Univariate GLM: Student's t -tests, regression, AN(C)OVA
 - Multivariate GLM: within-subject factors
 - LME: linear mixed-effects model
 - MEMA: mixed-effects multilevel analysis
 - BML (Bayesian multilevel model)

Terminology: categorical vs quantitative

- Factors
 - Number of levels: categories
 - Within-subject (repeated-measures): tasks, conditions
 - Between-subjects
 - Patients/controls, sex, genotypes, scanners/sites, handedness, ...
 - Each subject nested within a group
 - Subjects: **random-effects factor** - measuring randomness
 - Of no interest: random samples from a population
- Quantitative variables
 - Numeric or continuous
 - Age, IQ, reaction time, brain volume, ...
 - 3 meanings of covariate
 - Quantitative
 - Of no interest: sex, qualitative (scanner/site, groups) or quantitative
 - Explanatory variable

Terminology: fixed vs random

- Fixed-effects variables
 - Of research interest
 - Population mean, visual vs auditory, age, ...
 - Unable to extend to something else: visual vs auditory => smell, touch
 - Modeled as **constants**, not random variables
 - Shared by all subjects
 - Not exchangeable/replaceable or extendable to something else
- Random-effects variables
 - Of research interest? $\hat{\beta}_i = b + \epsilon_i, \epsilon_i \sim N(0, \sigma^2)$
 - Subjects: random samples
 - Trials, regions, scanners/sites?
 - Modeled as **random variables**: Gaussian distributions
 - Exchangeable (vs independent), replaceable, generalizable
- Differentiations blurred under BML

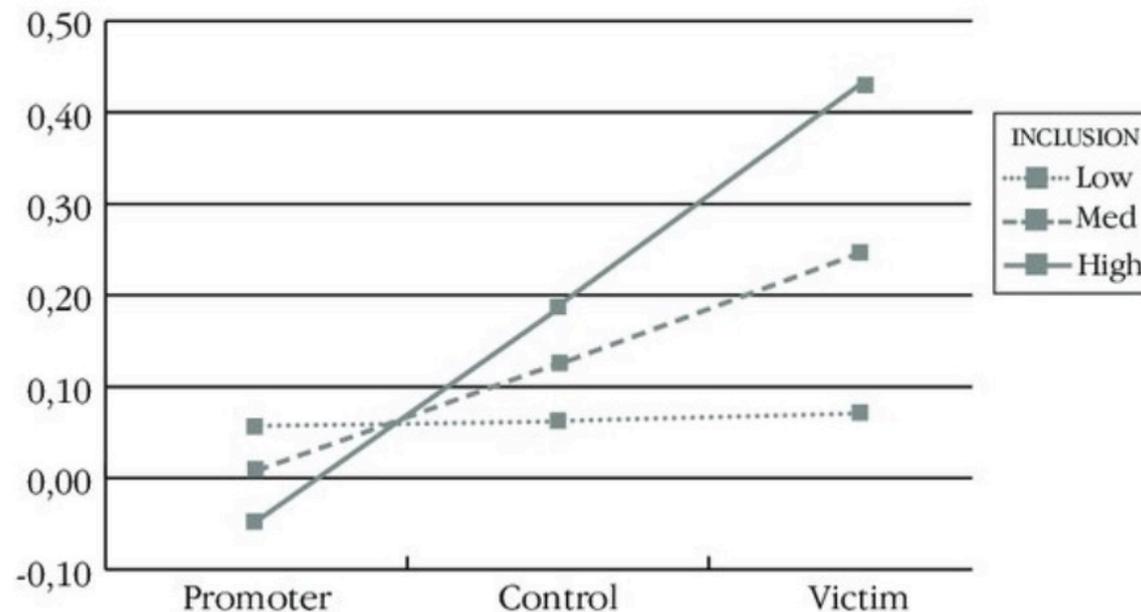
Terminology: main effects

- Main effect for a fixed-effects factor
 - Omnibus: overall inference or summarization
 - Evidence for differences across 3 levels
 - Conventional ANOVA framework
 - F -statistic: not detailed enough
 - Further partitions: post hoc inferences via pairwise comparisons
 - F -statistic as a two-sided test?
 - 1) $A > B$, 2) $A < B$, 3) $A \neq B$

Terminology: interactions

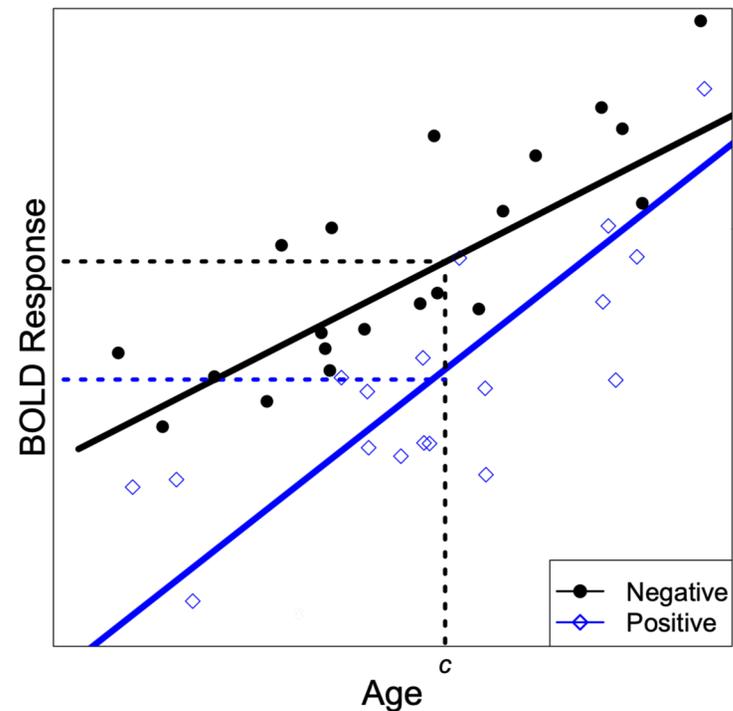
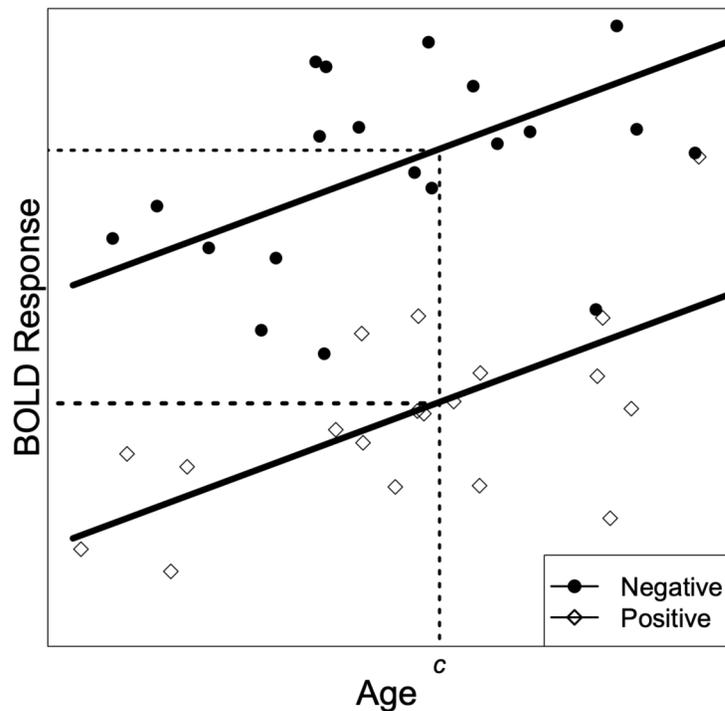
- Interaction effects between 2 or more factor
 - Omnibus: overall inference or summarization
 - Conventional ANOVA framework
 - F -statistic: not detailed enough
 - Further partitions: post hoc inferences via pairwise comparisons
 - 2×2 design: **difference of difference**
 - F -test for interaction = t -test of

$(A1B1 - A1B2) - (A2B1 - A2B2)$ or $(A1B1 - A2B1) - (A1B2 - A2B2)$



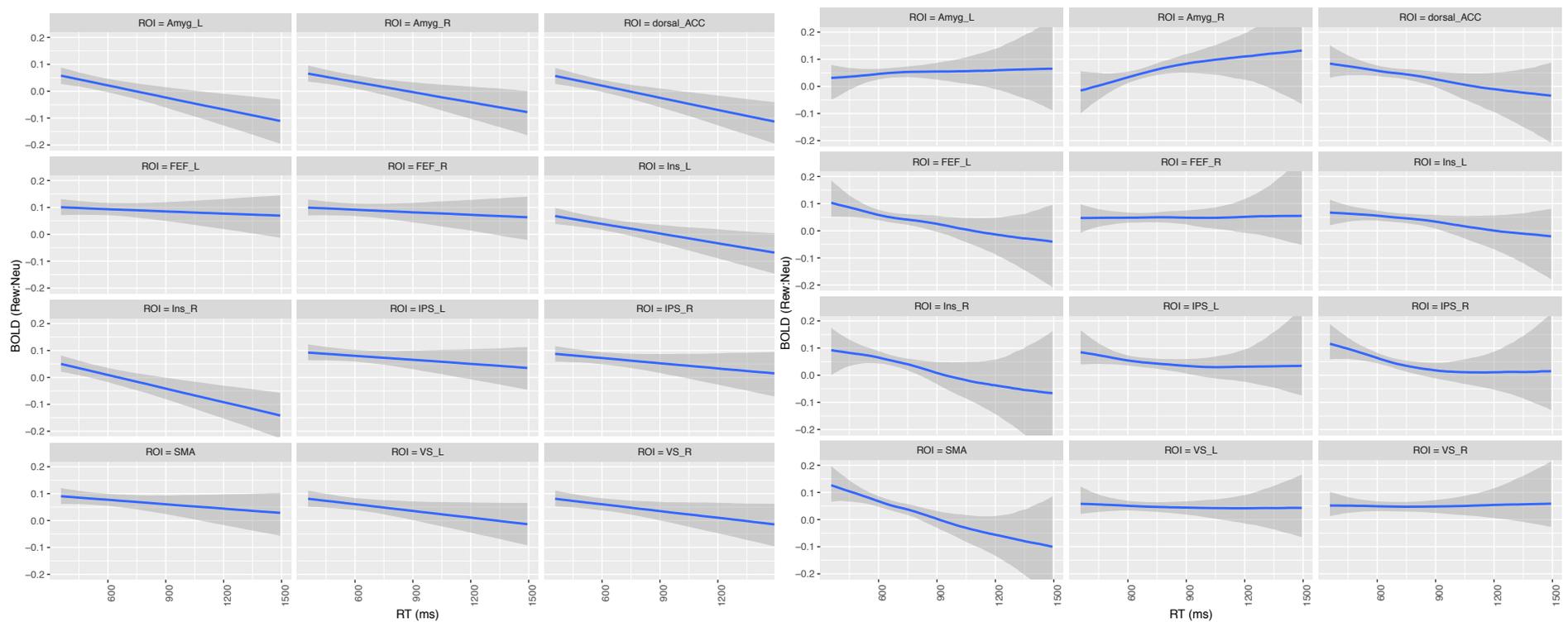
Terminology

- Interaction effects involving a quantitative variable
 - By default: linearity (age, RT modulation, ...)
 - Controlling: misconception - covariate out or regress out?
 - Effect of interest
 - Interaction between a factor and a quantitative variable



Terminology

- Interaction effect involving a quantitative variable
 - Validity of linearity
 - Nonlinear: difficult! Polynomials? Theory-driven?



Example: 2 × 3 Mixed ANCOVA

- Explanatory variables
 - Factor A (**Group**): 2 levels (patient and control)
 - Factor B (**Condition**): 3 levels (pos, neg, neu)
 - Factor S (**Subject**): 15 ASD children and 15 healthy controls
 - Quantitative **covariate**: **Age**
- Piecemeal: multiple *t*-tests – too tedious
 - Group comparison + age effect
 - Pairwise comparisons among three conditions
 - Assumption: same age effect across conditions
 - Difficulties with *t*-tests
 - Main effect of Condition: 3 levels plus age?
 - Interaction between Group and Condition
 - Age effect across three conditions?

Classical ANOVA: 2 × 3 Mixed ANOVA

- Factor A (**Group**): 2 levels (patient and control)
- Factor B (**Condition**): 3 levels (pos, neg, neu)
- Factor S (**Subject**): 15 ASD children and 15 healthy controls
- Covariate (**Age**): **cannot** be modeled; **no** correction for sphericity violation

$$F_{(a-1, a(n-1))}(A) = \frac{MSA}{MSS(A)},$$

$$F_{(b-1, a(b-1)(n-1))}(B) = \frac{MSB}{MSE},$$

$$F_{((a-1)(b-1), a(b-1)(n-1))}(AB) = \frac{MSAB}{MSE}$$

where

$$MSA = \frac{SSA}{a-1} = \frac{1}{a-1} \left(\frac{1}{bn} \sum_{j=1}^a Y_{.j}^2 - \frac{1}{abn} Y_{...}^2 \right),$$

$$MSB = \frac{SSB}{b-1} = \frac{1}{b-1} \left(\frac{1}{an} \sum_{k=1}^b Y_{..k}^2 - \frac{1}{abn} Y_{...}^2 \right),$$

$$MSAB = \frac{SSAB}{(a-1)(b-1)} = \frac{1}{(a-1)(b-1)} \left(\frac{1}{n} \sum_{j=1}^a \sum_{k=1}^b Y_{.jk} - \frac{1}{bn} \sum_{j=1}^a Y_{.j}^2 - \frac{1}{an} \sum_{k=1}^b Y_{..k}^2 + \frac{1}{abn} Y_{...}^2 \right),$$

$$MSS(A) = \frac{SSS(A)}{a(n-1)} = \frac{1}{a(n-1)} \left(\frac{1}{b} \sum_{i=1}^n \sum_{j=1}^a Y_{ij.}^2 - \frac{1}{bn} \sum_{j=1}^a Y_{.j}^2 \right),$$

$$MSE = \frac{1}{a(b-1)(n-1)} \left(\sum_{i=1}^n \sum_{j=1}^a \sum_{k=1}^b Y_{ijk}^2 - \frac{1}{n} \sum_{j=1}^a \sum_{k=1}^b Y_{.jk} - \frac{1}{b} \sum_{i=1}^n \sum_{j=1}^a Y_{ij.}^2 + \frac{1}{bn} \sum_{j=1}^a Y_{.j}^2 + \frac{1}{abn} Y_{...}^2 \right)$$

3dANOVA3 –type 5 (equal # of subjects across groups)

Univariate GLM: 2 x 3 mixed ANOVA

- Group: 2 levels (patient and control)
- Condition: 3 levels (pos, neg, neu)
- Subject: 3 ASD children and 3 healthy controls

Difficult to incorporate covariates

- Broken orthogonality of matrix

No correction for sphericity violation

$$\begin{matrix}
 \text{Subj} \\
 1 \\
 1 \\
 1 \\
 2 \\
 2 \\
 2 \\
 3 \\
 3 \\
 3 \\
 4 \\
 4 \\
 4 \\
 5 \\
 5 \\
 5 \\
 6 \\
 6 \\
 6
 \end{matrix}
 \begin{pmatrix}
 \beta_{11} \\
 \beta_{12} \\
 \beta_{13} \\
 \beta_{21} \\
 \beta_{22} \\
 \beta_{23} \\
 \beta_{31} \\
 \beta_{32} \\
 \beta_{33} \\
 \beta_{41} \\
 \beta_{42} \\
 \beta_{43} \\
 \beta_{51} \\
 \beta_{52} \\
 \beta_{53} \\
 \beta_{61} \\
 \beta_{62} \\
 \beta_{63}
 \end{pmatrix}
 =
 \begin{pmatrix}
 X_0 & X_1 & X_2 & X_3 & X_4 & X_5 & X_6 & X_7 & X_8 & X_9 \\
 1 & 1 & 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\
 1 & 1 & 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 \\
 1 & 1 & -1 & -1 & -1 & -1 & 1 & 0 & 0 & 0 \\
 1 & 1 & 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
 1 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 0 \\
 1 & 1 & -1 & -1 & -1 & -1 & 0 & 1 & 0 & 0 \\
 1 & 1 & 1 & 0 & 1 & 0 & -1 & -1 & 0 & 0 \\
 1 & 1 & 0 & 1 & 0 & 1 & -1 & -1 & 0 & 0 \\
 1 & 1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 \\
 1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & 1 & 0 \\
 1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & 1 & 0 \\
 1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & 1 & 0 \\
 1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & 0 & 1 \\
 1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & 0 & 1 \\
 1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & 0 & 1 \\
 1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & -1 & -1 \\
 1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & -1 & -1 \\
 1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & -1 & -1
 \end{pmatrix}
 \begin{pmatrix}
 \alpha_0 \\
 \alpha_1 \\
 \alpha_2 \\
 \alpha_3 \\
 \alpha_4 \\
 \alpha_5 \\
 \alpha_6 \\
 \alpha_7 \\
 \alpha_8 \\
 \alpha_9
 \end{pmatrix}
 +
 \begin{pmatrix}
 \delta_{11} \\
 \delta_{12} \\
 \delta_{13} \\
 \delta_{21} \\
 \delta_{22} \\
 \delta_{23} \\
 \delta_{31} \\
 \delta_{32} \\
 \delta_{33} \\
 \delta_{41} \\
 \delta_{42} \\
 \delta_{43} \\
 \delta_{51} \\
 \delta_{52} \\
 \delta_{53} \\
 \delta_{61} \\
 \delta_{62} \\
 \delta_{63}
 \end{pmatrix}$$

Univariate GLM: problematic implementations

Two-way **mixed** ANOVA

Between-subjects Factor A (**Group**): 2 levels (patient, control)

Within-subject Factor B (**Condition**): 3 levels (pos, neg, neu)

1) Omnibus tests

$$\begin{array}{l} F_A = \frac{MSA}{MSA(C)}, \\ F_B = \frac{MSB}{MSE}, \\ F_{AB} = \frac{MSAB}{MSE} \end{array} \quad \leftarrow \text{Correct} \quad \begin{array}{l} F_A = \frac{MSA}{MSE}, \\ F_B = \frac{MSB}{MSE}, \\ F_{AB} = \frac{MSAB}{MSE} \end{array} \quad \leftarrow \text{Incorrect}$$

2) Post hoc tests (contrasts)

- **Incorrect** *t*-tests for factor A due to incorrect denominator
- **Incorrect** *t*-tests for factor B or interaction effect AB when weights do not add up to 0

Univariate GLM: problematic implementations

Two-way **repeated-measures** ANOVA

Within-subjects Factor A (**Object**): 2 levels (house, face)

Within-subject Factor B (**Condition**): 3 levels (pos, neg, neu)

1) Omnibus tests

$$\begin{array}{l} F_A = \frac{MSA}{MSAC}, \\ F_B = \frac{MSB}{MSBC}, \\ F_{AB} = \frac{MSAB}{MSE} \end{array} \quad \text{Correct}$$
$$\begin{array}{l} F_A = \frac{MSA}{MSE}, \\ F_B = \frac{MSB}{MSE}, \\ F_{AB} = \frac{MSAB}{MSE} \end{array} \quad \text{Incorrect}$$

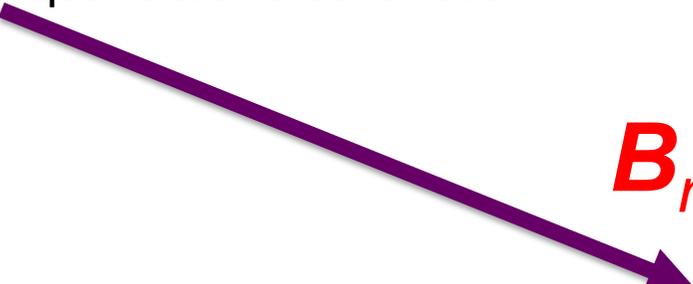
2) Post hoc tests (contrasts)

- **Incorrect** *t*-tests for both factors A and B due to incorrect denominator
- **Incorrect** *t*-tests for interaction effect AB if weights don't add up to 0

Better Approach: Multivariate GLM

- **Group**: 2 levels (patient and control)
- **Condition**: 3 levels (pos, neg, neu)
- **Subject**: 3 ASD children and 3 healthy controls
- **Age**: quantitative covariate

$$B_{n \times m} = X_{n \times q} A_{q \times m} + D_{n \times m}$$



<i>Subj</i>	<i>Pos</i>	<i>Neg</i>	<i>Neu</i>	<i>Int</i>	<i>Grp</i>	<i>Age</i>	<i>Pos</i>	<i>Neg</i>	<i>Neu</i>	<i>Subj</i>
1	β_{11}	β_{12}	β_{13}	1	1	-6	α_{01}	α_{02}	α_{03}	1
2	β_{21}	β_{22}	β_{23}	1	1	10	α_{11}	α_{12}	α_{13}	2
3	β_{31}	β_{32}	β_{33}	1	1	4	α_{21}	α_{22}	α_{23}	3
4	β_{41}	β_{42}	β_{43}	1	-1	-4				4
5	β_{51}	β_{52}	β_{53}	1	-1	-1				5
6	β_{61}	β_{62}	β_{63}	1	-1	-3				6

Chen et al. (2014). Applications of Multivariate Modeling to Neuroimaging Group Analysis: A Comprehensive Alternative to Univariate General Linear Model. *NeuroImage* 99:571-588.

MVM Implementation in AFNI

- Program **3dMVM**
 - No dummy coding needed!
 - **Symbolic coding** for variables and post hoc testing

```
3dMVM -prefix      OutputFile -jobs 8 -SC
      -bsVars      'Grp*Age'    -wsVars 'Cond' -qVars 'Age'
      -num_glt 4
      -gltLabel 1  Pat_Pos      -gltCode 1      'Grp : 1*Pat Cond : 1*Pos'
      -gltLabel 2  Ctl_Pos-Neg -gltCode 2      'Grp : 1*Ctl Cond : 1*Pos -1*Neg'
      -gltLabel 3  GrpD_Pos-Neg -gltCode 3      'Grp : 1*Ctl -1*Pat Cond : 1*Pos -1*Neg'
      -gltLabel 4  Pat_Age      -gltCode 4      'Grp : 1*Pat Age :'
```

```
-dataTable
Subj      Grp      Age      Cond      InputFile
S1         Ctl      23      Pos      S1_Pos.nii
S1         Ctl      23      Neg      S1_Neg.nii
S1         Ctl      23      Neu      S1_Neu.nii
...
S50        Pat      19      Pos      S50_Pos.nii
S50        Pat      19      Neg      S50_Neg.nii
S50        Pat      19      Neu      S50_Neu.nii
```

Variable types

Post hoc tests

Data layout

Improvement 1: precision information

- Conventional approach: β_s as response variable
 - Assumptions
 - no measurement errors
 - all subjects have same precision
 - All subjects are treated equally
- More precise method: β_s and their t -stats as input
 - t -statistic contains precision
 - β_s and their t -stats as input
 - Only available for GLM types: 3dMEMA
 - Regions with substantial cross-subject variability
- Best approach: combining all subjects in one big model
 - Currently not feasible

Chen et al. (2012). FMRI Group Analysis Combining Effect Estimates and Their Variances. NeuroImage 60:747-765.

One group: Example

- 3dttest++: β as input only

```
3dttest++ -prefix Vis -mask mask+tlrc -zskip \
  -setA 'FP+tlrc[Vrel#0_Coef]' \
  'FR+tlrc[Vrel#0_Coef]' \
  .....
  'GM+tlrc[Vrel#0_Coef]'
```

Voxel value = 0 → treated it as missing

- 3dMEMA: β and t -statistic as input

```
3dMEMA -prefix VisMEMA -mask mask+tlrc -setA Vis \
  FP 'FP+tlrc[Vrel#0_Coef]' 'FP+tlrc[Vrel#0_Tstat]' \
  FR 'FR+tlrc[Vrel#0_Coef]' 'FR+tlrc[Vrel#0_Tstat]' \
  .....
  GM 'GM+tlrc[Vrel#0_Coef]' 'GM+tlrc[Vrel#0_Tstat]' \
  -missing_data 0
```

Voxel value = 0 → treated it as missing

Paired comparison: Example

- 3dttest++: comparing two conditions

```
3dttest++ -prefix Vis_Aud \
-mask mask+tlrc -paired -zskip \
-setA 'FP+tlrc[Vrel#0_Coef]' \
      'FR+tlrc[Vrel#0_Coef]' \
.....
      'GM+tlrc[Vrel#0_Coef]' \
-setB 'FP+tlrc[Arel#0_Coef]' \
      'FR+tlrc[Arel#0_Coef]' \
.....
      'GM+tlrc[Arel#0_Coef]'
```

Paired Comparison: Example

- 3dMEMA: accounting for differential accuracy
 - Contrast as input

```
3dMEMA -prefix Vis_Aud_MEMA \
-mask mask+tlrc -missing_data 0 \
-setA Vis-Aud \
FP 'FP+tlrc[Vrel-Arel#0_Coef]' 'FP+tlrc[Vrel-Arel#0_Tstat]' \
FR 'FR+tlrc[Vrel-Arel#0_Coef]' 'FR+tlrc[Vrel-Arel#0_Tstat]' \
.....
GM 'GM+tlrc[Vrel-Arel#0_Coef]' 'GM+tlrc[Vrel-Arel#0_Tstat]'
```

Improvement 2: more accurate HDR

- Conventional approach $f(t) = t^q e^{-t} / (q^q e^{-q})$ ($q=4$)
 - Presumed curve (empirical and approximate): BLOCK(d,1)
 - Fixing HDR shape and capturing magnitude with one number
 - Simple and straightforward: one β per effect
 - Not ideal: HDR varies across regions, tasks/conditions, groups, subjects
- More accurate HDR modeling
 - Data driven (no assumptions about HDR shape): TENTzero, CSPLINzero
 - Estimating both shape and magnitude with multiple effect estimates
 - More complicated: multiple β s per task/condition
 - More challenging: how to make inferences? $H_0: \beta_1=0, \beta_2=0, \dots, \beta_k=0$
- Middle
 - Adjust major HDR curve with 2/3 auxiliary functions: SPMG2/3
 - Focus: magnitude (β) associated with major HDR curve

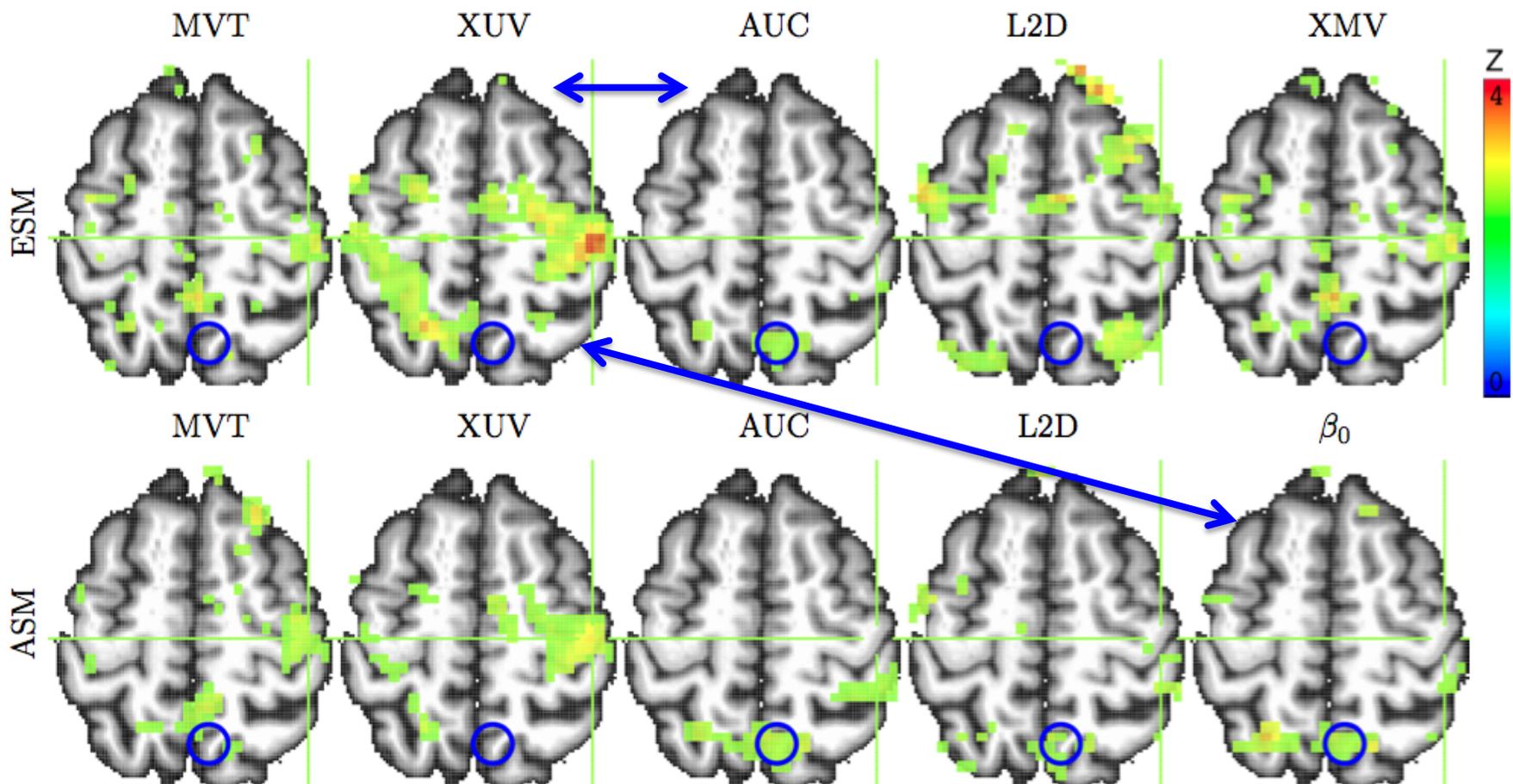
Improvement 2: more accurate HDR

- Group analysis with HDR estimates: TENTzero, CSPLINzero
 - NHST: $H_0: \beta_1=0, \beta_2=0, \dots, \beta_k=0$
 - Area under curve (AUC) approach
 - Reduce to one number: use area as magnitude approximation
 - Ignore **shape** subtleties
 - Shape information loss: (undershoot, peak location/width)
 - Better approach: maintaining shape integrity
 - Take individual β s to group analysis (MVM)
 - One group with one condition: 3dLME
 - Other scenarios: treat β s as levels of a factor (e.g., Time) - 3dMVM
 - ** Task or group effect: F -stat for interaction between task group and Time, complemented with main effect for task/group (AUC)

Chen et al. (2015). Detecting the subtle shape differences in hemodynamic responses at the group level. *Front. Neurosci.*, 26 October 2015.

Improvement 2: more accurate HDR

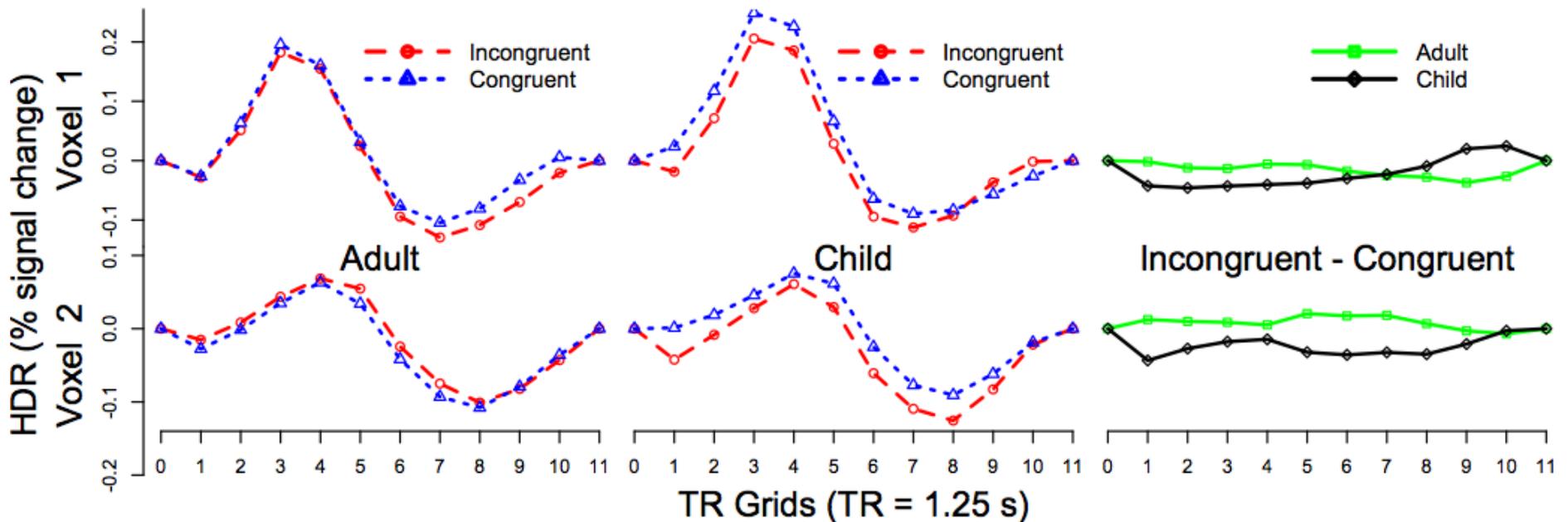
- 2 groups (children, adults), 2 conditions (congruent, incongruent), 1 quantitative covariate (age)
- 2 methods: HRF modeled by 10 (tents) and 3 (SPMG3) bases
- Effect of interaction: interaction group:condition – **3dMVM**



Improvement 2: more accurate HDR

- Advantages of ESM over FSM
 - More likely to detect HDR shape subtleties
 - Visual verification of HDR signature shape (vs. relying on significance testing: p -values)

Study: Adults/Children with Congruent/Incongruent stimuli (2×2)



Improvement 3: complex situations - LME

- Missing data
 - Missing at subject level: Longitudinal study
 - Missing at random: unrelated to effect of interest
 - GLM would not work
- Within-subject covariate: random slope
 - Reaction time across multiple conditions
 - Age in longitudinal study
 - Random slope: varying covariate effect across subjects
- Hierarchical data
 - Subjects, families, groups
 - Subjects are genetically related in multilevel structure
 - Adolescent Brain Cognitive Development (ABCD) Study

Chen et al. (2013). Linear Mixed-Effects Modeling Approach to fMRI Group Analysis. *NeuroImage* 73:176-190.

Dealing with quantitative variables

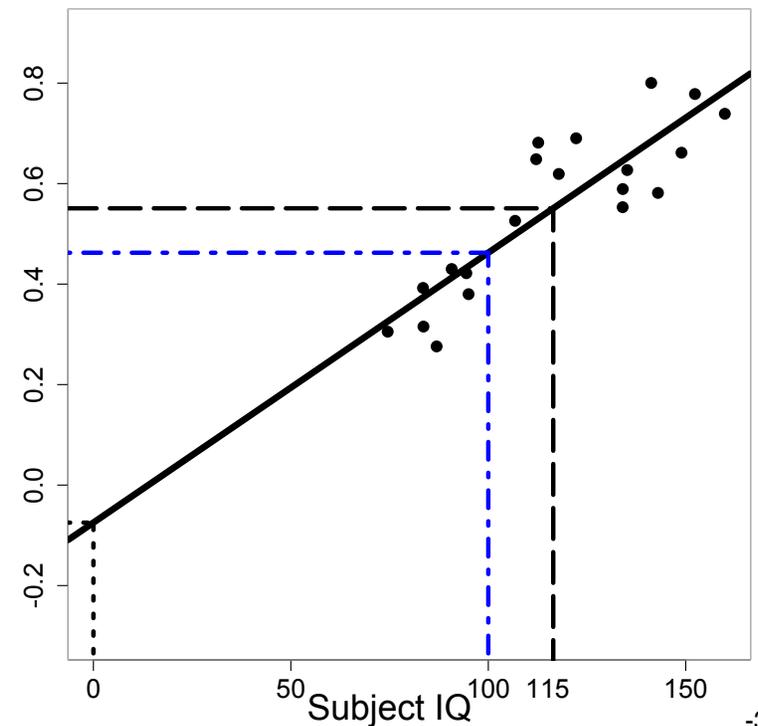
- Reasons to consider a covariate
 - Effect of interest
 - Model improvement: accounting for data variability
- Frameworks
 - ANCOVA: between-subjects factor (e.g., group) + quantitative variable
 - Broader frameworks: regression, GLM, MVM, LME, BML
 - Assumptions: linearity, homogeneity of slopes (interaction)
- Interpretations
 - Effect of interest: slope, rate, marginal effect
 - Regress/covariate out x ? Head motion at individual level
 - “Controlling x at ...”, “holding x constant”: centering

Quantitative variables: centering

- Model

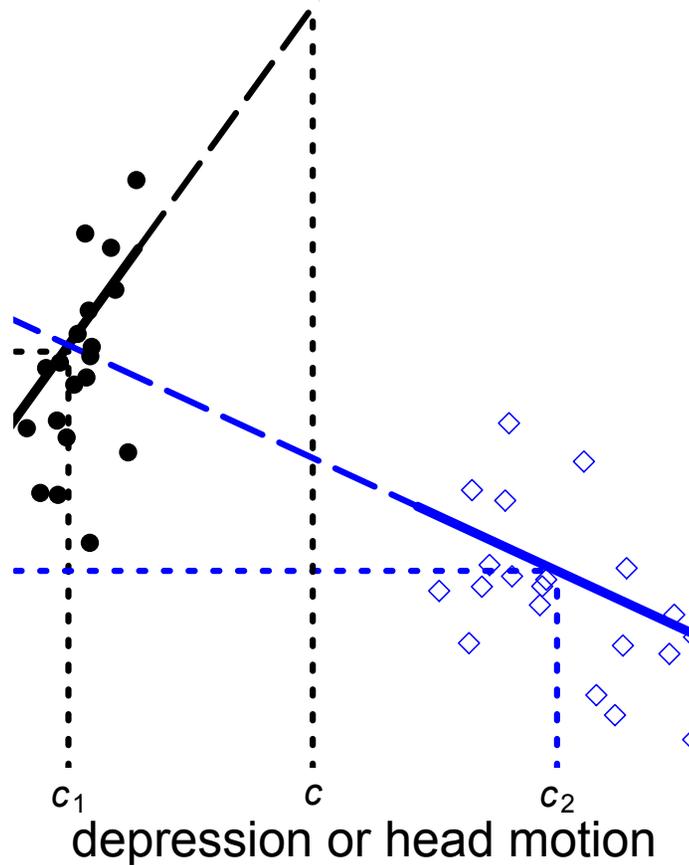
$$\hat{\beta}_i = \alpha_0 + \alpha_1 * x_{1i} + \alpha_2 * x_{2i} + \epsilon_i$$

- α_1, α_2 - slope
- α_0 – intercept: group effect when $x = 0$
 - Not necessarily meaningful
 - Linearity may not hold
 - Centering for interpretability
 - Centering around: mean, median, or something else



Quantitative variables: centering

- When a factor is involved
 - Complicated: within-level or grand centering



<https://afni.nimh.nih.gov/pub/dist/doc/html/doc/STATISTICS/center.html>

IntraClass Correlation (ICC)

- Reliability (consistency, agreement/reproducibility) across two or more measurements of a condition/task
 - sessions, scanners, sites, studies, twins
 - Classic example (Shrout and Fleiss, 1979): n targets are rated by k raters
 - Relationship with Pearson correlation
 - Pearson correlation: two **different** types of measure: e.g., BOLD response vs. RT
 - ICC: **same** measurement (intraclass)
 - Modeling frameworks: ANOVA, LME
 - 3 types ICC: ICC(1,1), **ICC(2,1)**, **ICC(3,1)** – one-, two-way random- and mixed-effects ANOVA

ICC implementations

- **Traditional** definition: one-way random-effects ANOVA

$$y_{ij} = b_0 + b_i + \lambda_j + \epsilon_{ij}$$

- Assumptions: subject $\lambda_j \sim G(0, \sigma_\lambda^2)$, $\epsilon_{ij} \sim G(0, \sigma_\epsilon^2)$
- **ICC(3,1)** estimated via ANOVA (Shrout & Fleis, 1979)

$$\hat{\rho}_3 = \frac{MS_\lambda - MS_\epsilon}{MS_\lambda + (k - 1)MS_\epsilon}$$

- Conceptualized as an LME model

$$\rho_3 = \frac{\sigma_\lambda^2}{\sigma_\lambda^2 + \sigma_\epsilon^2}$$

- Whole-brain voxel-level ICC
 - ICC(2,1): **3dLME -ICC** or **3dLME -ICCb**
 - **3dICC**: ICC(1,1), ICC(2,1) and ICC(3,1)
 - Covariates can be incorporated

Chen et al. (2017), Intraclass correlation: Improved modeling approaches and applications for neuroimaging. Human Brain Mapping 39(3): 1187-1206.

Naturalistic scanning

- Subjects view a natural scene during scanning
 - Visuoauditory movie clip (e.g., <http://studyforrest.org/>)
 - Music, speech, games, ...
- Duration: a few minutes or more
- Close to naturalistic settings: minimally manipulated
- Effect of interest: inter-subject correlation (ISC) – 3dTcorrelate
 - Extent of [synchronization/entrainment](#)
- Whole-brain voxel-wise analysis: 3dISC

[Hasson et al., 2004](#). Intersubject synchronization of cortical activity during natural vision. *Science* 303:1634-1640.

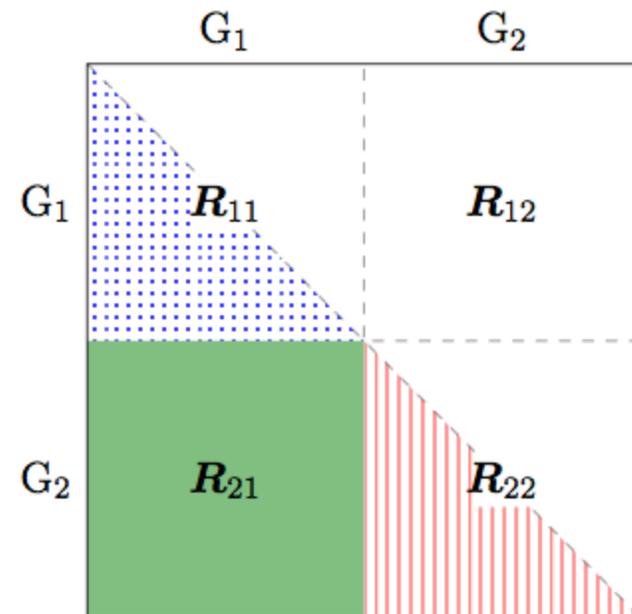
ISC group analysis

- Voxel-wise ISC matrix (usually Fisher-transformed)
 - One group

$$\mathbf{R}^{(n)} = \begin{matrix} & S_1 & S_2 & S_3 & \cdots & S_n \\ \begin{matrix} S_1 \\ S_2 \\ S_3 \\ \vdots \\ S_n \end{matrix} & \begin{pmatrix} 1 & r_{12} & r_{13} & \cdots & r_{1n} \\ r_{21} & 1 & r_{23} & \cdots & r_{2n} \\ r_{31} & r_{32} & 1 & \cdots & r_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ r_{n1} & r_{n2} & r_{n3} & \cdots & 1 \end{pmatrix} \end{matrix}$$

$$\mathbf{Z}^{(n)} = \begin{matrix} & S_1 & S_2 & S_3 & \cdots & S_n \\ \begin{matrix} S_1 \\ S_2 \\ S_3 \\ \vdots \\ S_n \end{matrix} & \begin{pmatrix} - & z_{12} & z_{13} & \cdots & z_{1n} \\ z_{21} & - & z_{23} & \cdots & z_{2n} \\ z_{31} & z_{32} & - & \cdots & z_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ z_{n1} & z_{n2} & z_{n3} & \cdots & - \end{pmatrix} \end{matrix}$$

- Two groups
 - Within-group ISC: R11, R22
 - Inter-group ISC: R21
 - 3 group comparisons: R11 vs R22, R11 vs R21, R22 vs R21



Complexity of ISC analysis

- 2 ISC values associated with a common subject are correlated with each other: 5 subjects, 10 ISC values
- $\rho \neq 0$ characterizes non-independent relationship

$$\begin{array}{c}
 Z_{21} \quad Z_{31} \quad Z_{41} \quad Z_{51} \quad Z_{32} \quad Z_{42} \quad Z_{52} \quad Z_{43} \quad Z_{53} \quad Z_{54} \\
 \begin{pmatrix}
 Z_{21} & 1 & \rho & \rho & \rho & \rho & \rho & \rho & 0 & 0 & 0 \\
 Z_{31} & \rho & 1 & \rho & \rho & \rho & 0 & 0 & \rho & \rho & 0 \\
 Z_{41} & \rho & \rho & 1 & \rho & 0 & \rho & 0 & \rho & 0 & \rho \\
 Z_{51} & \rho & \rho & \rho & 1 & 0 & 0 & \rho & 0 & \rho & \rho \\
 Z_{32} & \rho & \rho & 0 & 0 & 1 & \rho & \rho & \rho & \rho & 0 \\
 Z_{42} & \rho & 0 & \rho & 0 & \rho & 1 & \rho & \rho & 0 & \rho \\
 Z_{52} & \rho & 0 & 0 & \rho & \rho & \rho & 1 & 0 & \rho & \rho \\
 Z_{43} & 0 & \rho & \rho & 0 & \rho & \rho & 0 & 1 & \rho & \rho \\
 Z_{53} & 0 & \rho & 0 & \rho & \rho & 0 & \rho & \rho & 1 & \rho \\
 Z_{54} & 0 & 0 & \rho & \rho & 0 & \rho & \rho & \rho & \rho & 1
 \end{pmatrix}
 \end{array}$$

- **Challenge:** how to handle this irregular correlation matrix?

Previous methods

- Student's t-test
 - Independence violation acknowledged but not accounted for
 - Justification via observations that “null data” (generated by ISC values with randomly shifted time series) followed $t(N-1)$
- Various nonparametric methods
 - • Permutations: null distribution via randomization across space (voxels) and time (e.g., circularly shifting each subject's time series by a random lag)
 - Matlab package: ISC Toolbox (Kauppi et al, 2014)
- Leave one out (LOO): Kauppi et al, 2010
 - Compute ISC of a subject between a voxel's BOLD time course in the subject and the average of that voxel's time course in the remaining subjects
 - Perform Student t-test on the LOO ISC values

Nonparametric methods

- Subject-wise bootstrapping
- Subject-wise permutations

Chen et al, 2016. Untangling the relatedness among correlations, part I: Nonparametric approaches to inter-subject correlation analysis at the group level. Neuroimage.

ISC: LME approach

- Modeling via effect partitioning: **crossed random-effects** LME

$$z_{ij} = b_0 + \theta_i + \theta_j + \epsilon_{ij}, \quad i \neq j$$

$$\theta_i, \theta_j \stackrel{iid}{\sim} G(0, \zeta^2) \quad \text{and} \quad \epsilon_{ij} \stackrel{iid}{\sim} G(0, \eta^2)$$

cross-subject

within-subject

- Characterizing the relatedness among ISCs via LME

$$\rho = \text{Corr}(z_{ij}, z_{jl}) = \frac{\text{Cov}(z_{ij}, z_{jl})}{\sqrt{\text{Var}(z_{ij})\text{Var}(z_{jl})}} = \frac{\zeta^2}{2\zeta^2 + \eta^2}$$

$$0 \leq \rho = \frac{\zeta^2}{2\zeta^2 + \eta^2} = \frac{\zeta^2}{\sigma^2} \leq 0.5$$

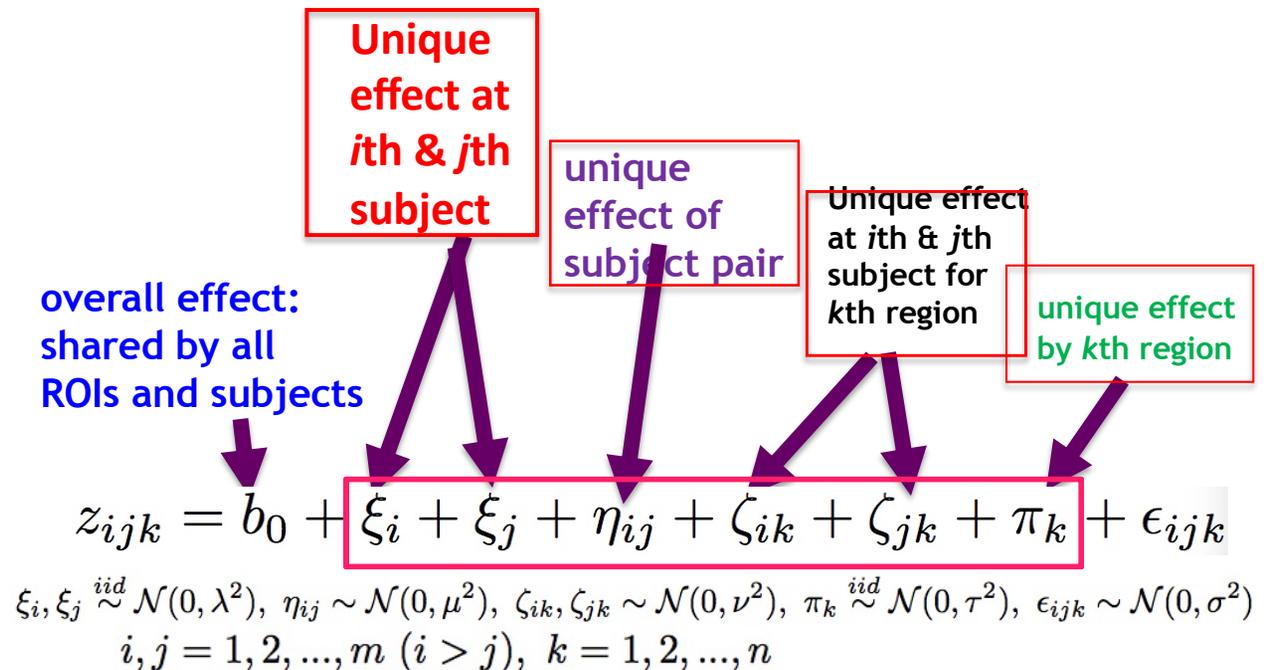
- 3dISC

Chen et al, 2017. Untangling the Relatedness among Correlations, Part II: Inter-Subject Correlation Group Analysis through Linear Mixed-Effects Modeling. *Neuroimage*. *NeuroImage* 147:825-840

Region-based ISC analysis through **BML**

- **One** model integrates all ROIs: BML
- ROIs loosely constrained instead of being unrelated
- Effects of interest

- **region**: $b_0 + \pi_k$
- **subject**: $b_0 + \xi_i$



Chen, G. et al., 2019. Untangling the Relatedness among Correlations, Part III: Extending Model Capabilities of Inter-Subject Correlation Analysis for Naturalistic Scanning. In press.

Program List

- **3dtttest++** (GLM: one-, two-sample, paired t , between-subjects variables)
- **3dMVM** (generic AN(C)OVA)
- **3dLME** (sophisticated cases: missing data, within-subject covariates)
- **3dMEMA** (similar to 3dtttest++: measurement errors)
- **3dICC** (intraclass correlation)
- **3dISC** (inter-subject correlation)
- **RBA** (region-based analysis)
- **MBA** (matrix-based analysis)
- **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)
- **3dtttest** (*obsolete*: one-sample, two-sample and paired t)
- **3dRegAna** (*obsolete*: regression/correlation, covariates)
- **GroupAna** (*obsolete*: up to four-way ANOVA)

Summary

- Concepts and terminology
- Group analysis approaches
 - GLM: 3dtttest++, 3dMEMA
 - GLM, ANOVA, ANCOVA: 3dMVM
 - LME: 3dLME
 - Presumed vs. estimated HDR
- Miscellaneous
 - Issues with covariates
 - Intra-Class Correlation (ICC)
 - Inter-Subject Correlation (ISC)