

Group Analysis

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Program List

- **3dttest++** (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 3dttest++: measurement errors)
- **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)
- **3dttest** (**obsolete**: one-sample, two-sample and paired t)
- **3dRegAna** (**obsolete**: regression/correlation, covariates)
- **GroupAna** (**obsolete**: up to four-way ANOVA)
- **3dICC** (intraclass correlation): prototype only
- **3dISC** (intersubject correlation): prototype only

Preview of Coming Attractions

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

Goal = Give outline of AFNI capabilities in group analyses

Decisions about complex situations require help

<https://afni.nimh.nih.gov/afni/community/board>

Why Group Analysis?

- Reproducibility and generalization
 - Summarization
 - Generalization: from current results to population level
 - Typically 10 or more subjects per group
 - Individualized inferences: pre-surgical planning, lie detection, ...
- One model combining both steps (single subject and group)?
 - + Ideal: less information loss, more accurate inferences
 - - Historical
 - - Computationally unmanageable, and very hard to set up
 - - Data quality check at individual level

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 of the betas: 0.40 or .90
 - Do we have strong evidence for the effect being nonzero?
- Statistical modeling perspective
 - Simplest GLM: one-sample t -test
$$\hat{\beta}_i = b + \epsilon_i, \epsilon_i \sim N(0, \sigma^2)$$
 - Statistical evidence - t -test: $\hat{b} / (\hat{\sigma} / n)$
 - summarization: b (dimensional), sd , and t (dimensionless)

Terminology

- Response/outcome variable: left-hand side of model
 - Regression β_i 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
- Type of 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
 - Finite (small) number of levels: categories (coded by labels)
 - Within-subject (repeated-measures): tasks, conditions
 - Between-subjects
 - patients/controls, genotypes, scanners/sites, handedness, ...
 - Each subject nested within a group
 - Subjects: **random-effects factor** - measuring randomness
 - Of no intrinsic interest: random samples from a population
- Quantitative variables
 - numeric or continuous
 - age, IQ, reaction time, brain volume, ...
 - 3 usages of “covariate”
 - No interest:
 - Qualitative (e.g., scanner/site, groups)
 - Quantitative (e.g., per subject amount of head motion)
 - Explanatory variable (e.g., subject age, anxiety score)

Terminology: fixed vs random

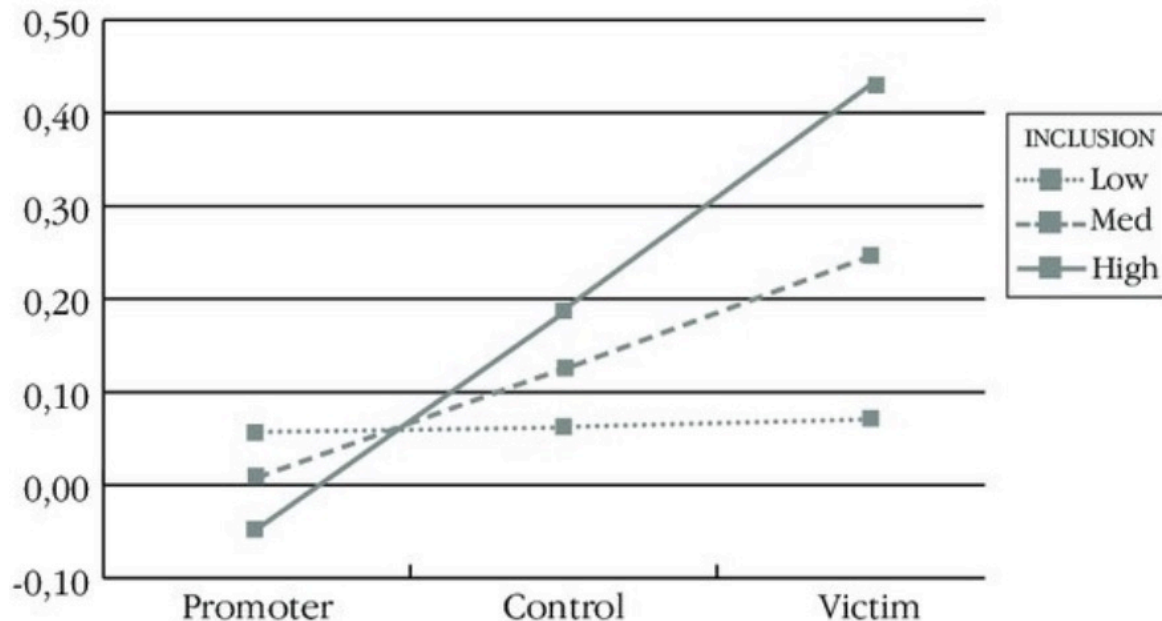
- Fixed-effects variables
 - Of research interest
 - Visual vs auditory, age, ...
 - Unable to extend to something else
 - Modeled as **constants**, not random variables
 - Shared by all subjects
 - Not exchangeable/replaceable or extendable to something else
- Random-effects variables (mean + random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

Terminology: main effects

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

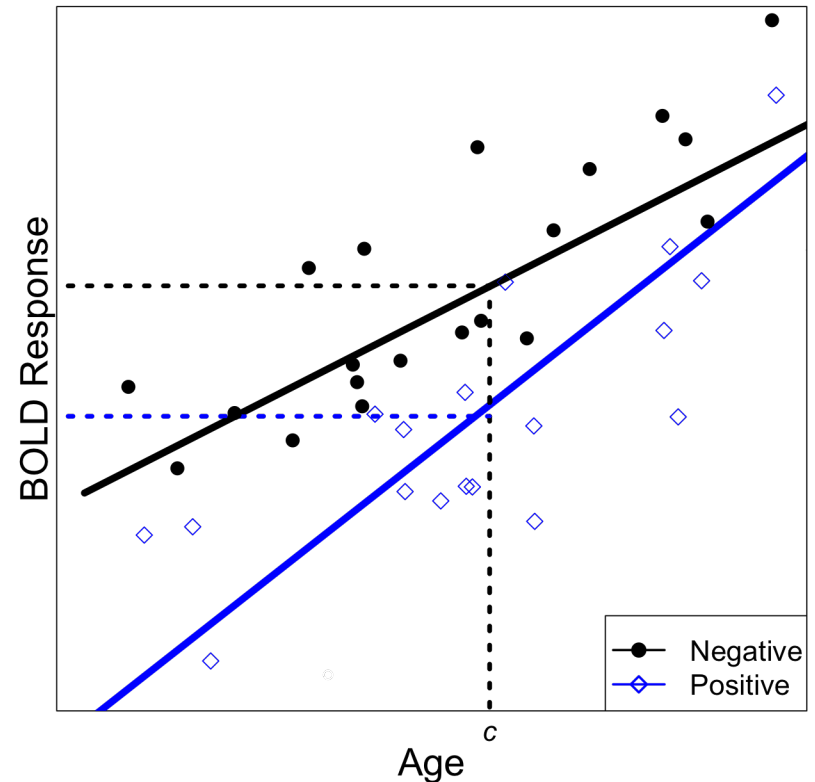
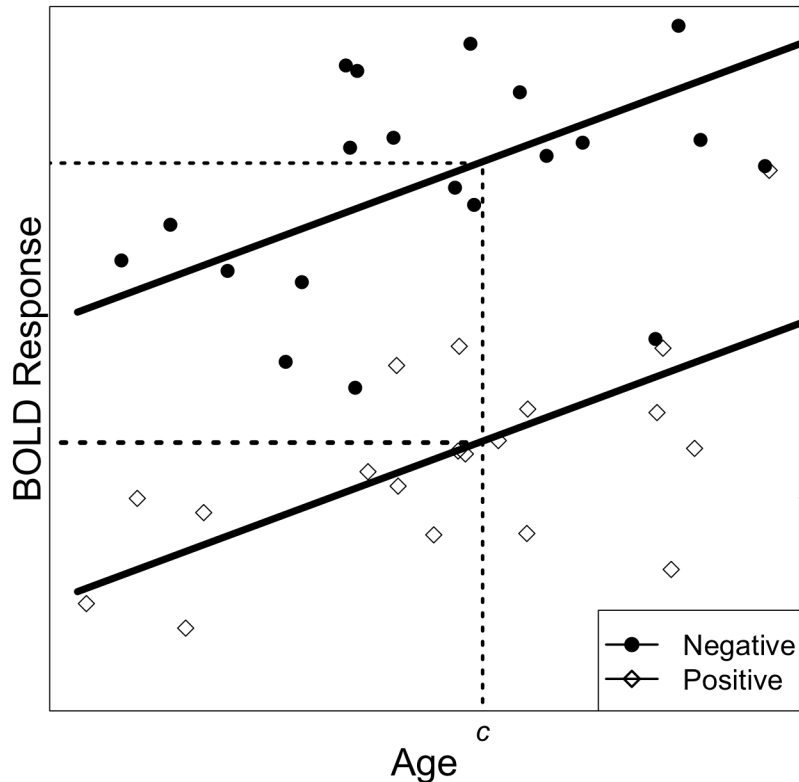
Terminology: interactions

- Interaction effect between 2 or more factors
 - Omnibus: overall inference or summarization
 - Conventional ANOVA framework
 - F -statistic: not detailed enough to tell what specifically is happening
 - Further partitions: post hoc inferences via pairwise comparisons
 - 2×2 design: difference of difference
 - F -test for 2×2 interaction = t -test of
 $(A1B1 - A1B2) - (A2B1 - A2B2)$ or $(A1B1 - A2B1) - (A1B2 - A2B2)$



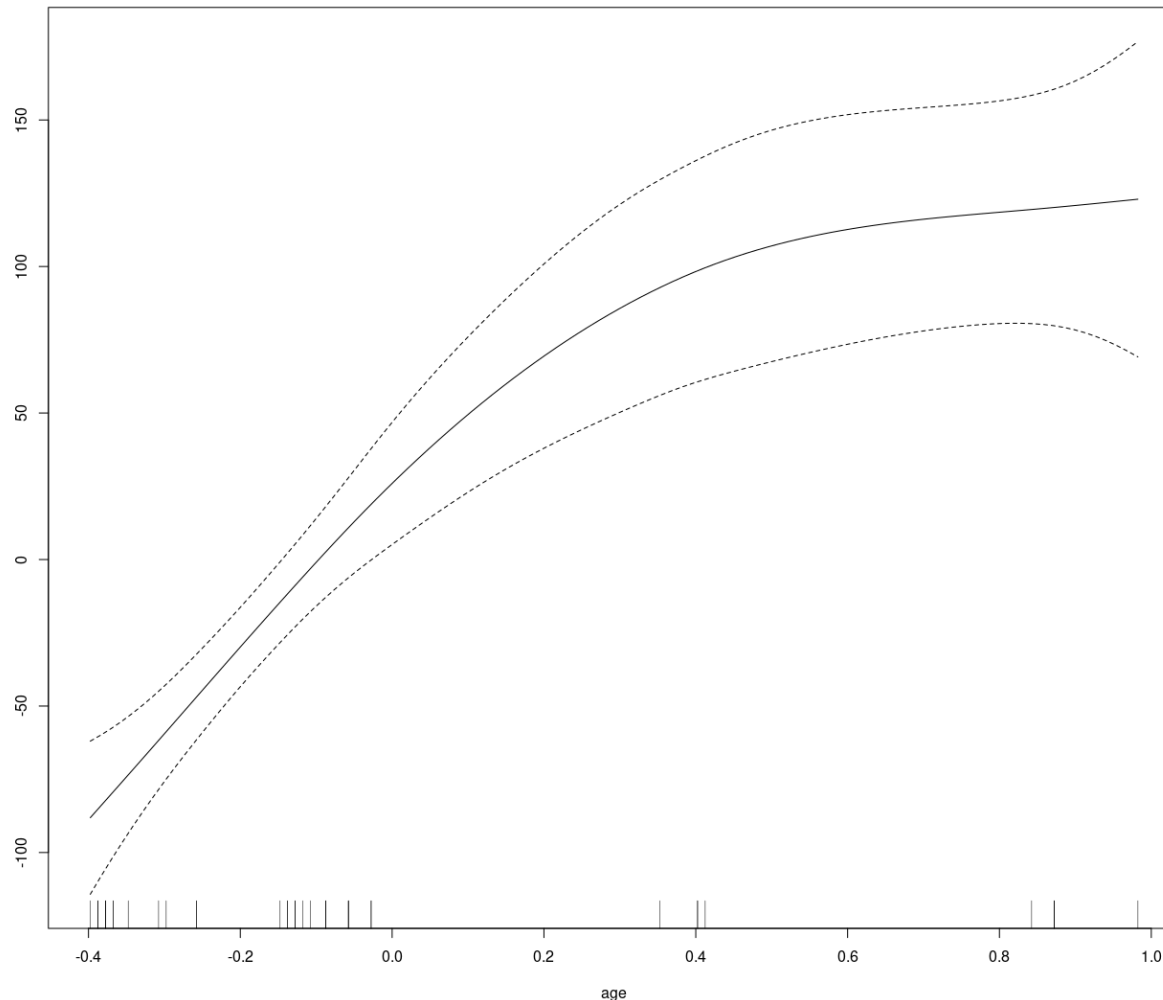
Terminology

- Interaction effect involving a quantitative variable
 - By default: linearity (age, modulation, ...)
 - Controlling: misconception – e.g., “covary out” age differences?
 - or, Effect of interest
 - Interaction between a factor and a quantitative variable



Terminology

- Interaction effect involving a quantitative variable
 - Validity of linearity of β with (e.g.) age
 - Nonlinear: difficult (too much freedom)! 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 – emotional words)
 - 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 (no covariate)

- 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

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

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

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

Different denominators

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

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

Univariate GLM: problematic implementations

(in some other software we won't name)

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

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

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

$$F_A = \frac{MSA}{MSAC},$$
$$F_B = \frac{MSB}{MSBC},$$
$$F_{AB} = \frac{MSAB}{MSE}$$

Correct

$$F_A = \frac{MSA}{MSE},$$
$$F_B = \frac{MSB}{MSE},$$
$$F_{AB} = \frac{MSAB}{MSE}$$

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

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

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

Data = betas

Model =
Design matrix =
Main Effect &
Group Coding
& Covariate

Fit
Parameters
(to be computed)

Residuals

MVM Implementation in AFNI

- Program **3dMVM** – generalize multi-way ANCOVA, and more
 - No dummy coding needed!
 - **Symbolic coding** for variables and post hoc testing

Variable types **Post hoc tests**

```
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
```

Data layout

MVM General Linear Tests - besides main effects

- **Symbolic coding** for variables and post hoc testing
 - **-bsVARS** '**Grp*Age**' shows 2 *between* subjects variables
 - **-qVars** '**Age**' shows one is quantitative (numbers)
 - So the other one **Grp** is categorical (labels)
 - **-wsVars** '**Cond**' shows 1 *within* subjects variable (categorical)
 - Potential values for all variables collated from data table
- **GLT #3** "**Grp : 1*Pat Cond : 1*Pos -1*Neg**"
 - Within the **Grp** variable, select the **Pat** mean effect
 - Within the **Cond** variable, select the difference between the **Pos** and **Neg** mean effects
 - **Age** is not specified, so test will be carried out on the effects regressed to the **Age** center (for each **Grp**)
- **GLT #4** "**Grp : 1*Pat Age :**" tests the *slope* of the betas w.r.t. **Age** for **Patients** (averaged across **Cond** values)

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 (have the same randomness)
- More precise method: estimated β_s plus precision estimates
 - t -statistic contains precision ($t = \beta / \text{SEM}(\beta)$)
 - β_s and their t -stats as input
 - β_s weighted based on precision
 - Only available for simple GLM types: 3dMEMA
 - Regions with substantial cross-subject variability
- Best approach: combining all subjects in one big super-model
 - Currently not feasible

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

- 3dtttest++: comparing two conditions

```
3dtttest++ -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 (among β s)
 - 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

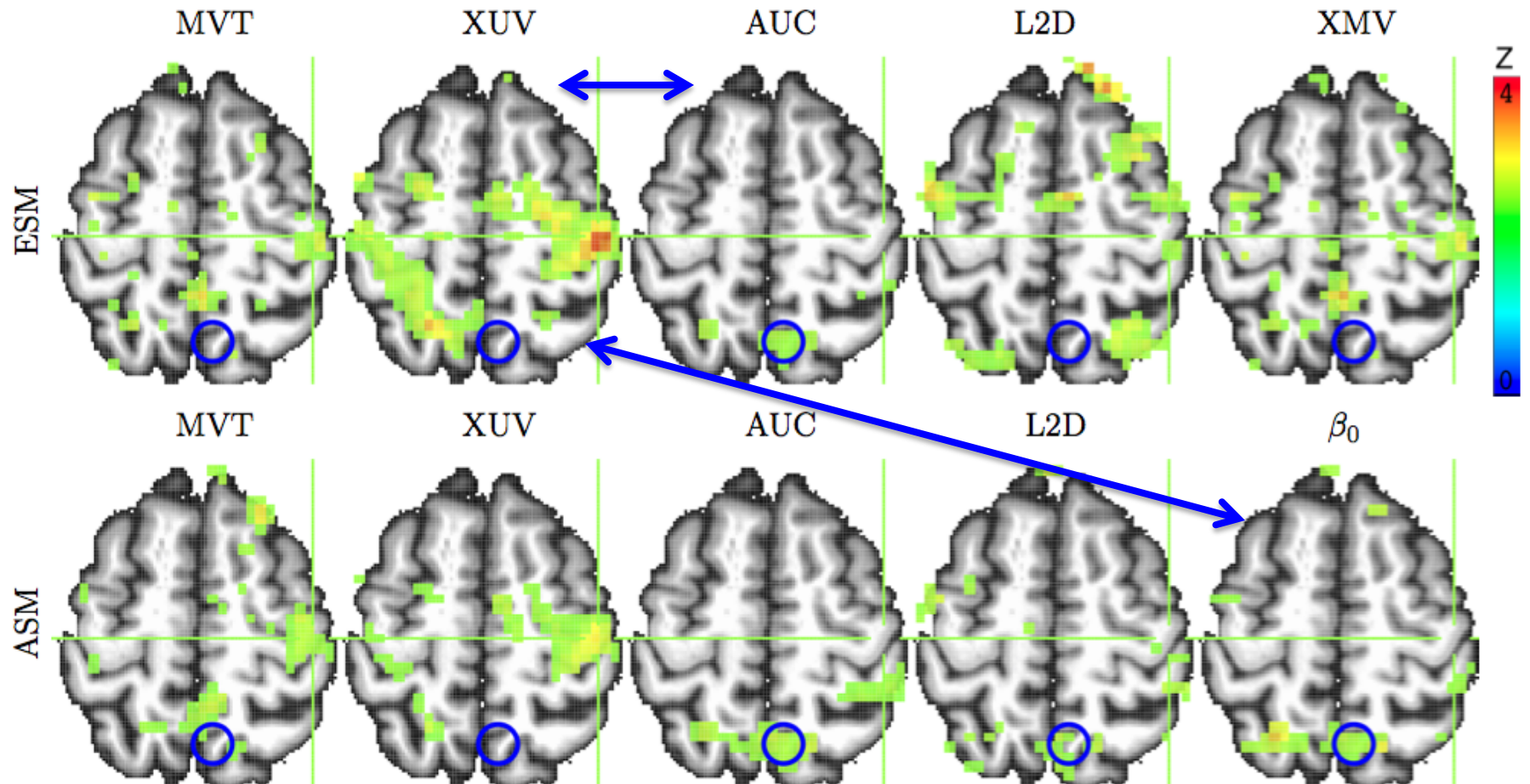
Improvement 2: more accurate HDR

- Group analysis with HDR estimates: TENTzero, CSPLINzero
 - NHST: $H_0: \beta_1=0, \beta_2=0, \dots, \beta_k=0$ [all responses in HRF = zero]
 - Area under curve (AUC) approach
 - Reduce HRF 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

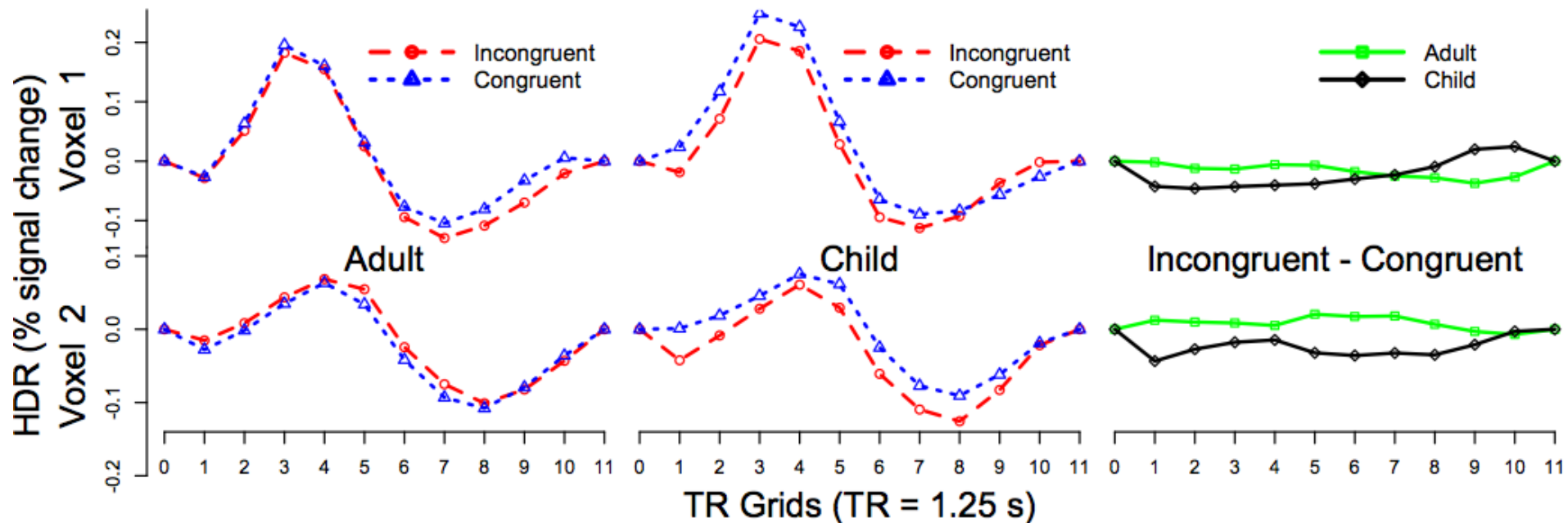
- 2 groups (children, adults), 2 conditions (congruent, incongruent), 1 quantitative covariate (age)
- 2 methods: HRF modeled by 10 (tents) and 3 (SPMG3) bases
- Effect of interaction: interaction group:condition – **3dMVM**



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)



Dealing with quantitative variables

- Reasons to consider a covariate
 - Effect of interest: variability of response with some subject parameter
 - Model improvement: accounting for data variability with plausible cause
 - But you don't particularly care about this effect *per se*
- 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 ? (e.g., head motion at individual level)
 - “Controlling x at ...”, “holding x constant”: *centering*

Quantitative variables: centering

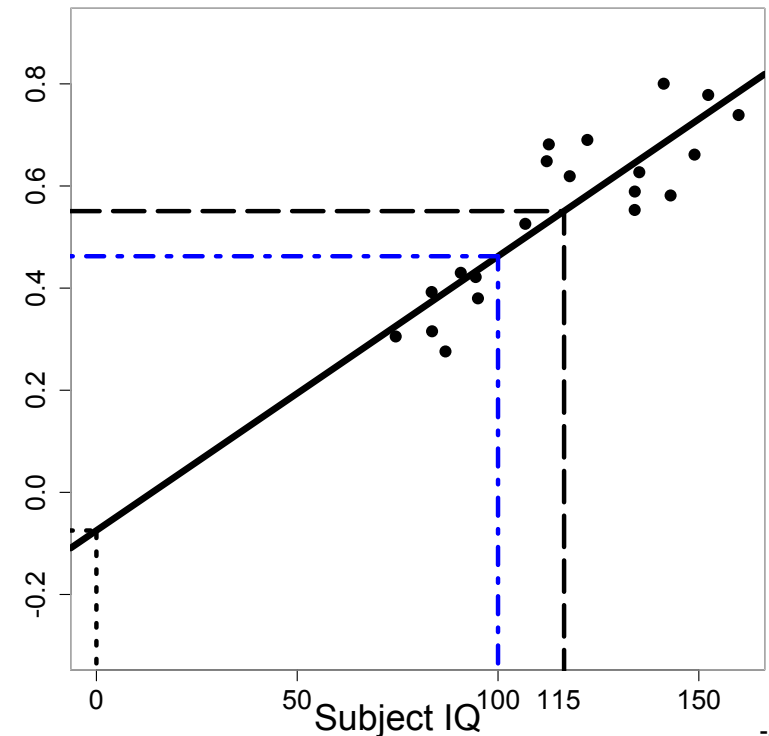
- Model

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

- α_1, α_2 - slope
- α_0 – intercept: group effect when $x=0$
 - Not necessarily meaningful by itself
 - Linearity may not hold over large ranges of x_1 or x_2
 - Centering covariates for interpretability
 - Mean or median centering?

- When a factor is involved

- Complicated decision: within-level or grand centering



A Useful Article about Covariates

- Miller GM and Chapman JP.
- Misunderstanding analysis of covariance
- J Abnormal Psych 110: 40-48 (2001)
- <http://dx.doi.org/10.1037/0021-843X.110.1.40>
- <http://psycnet.apa.org/journals/abn/110/1/40.pdf>

IntraClass Correlation (ICC)

- Reliability (consistency, agreement/reproducibility) across two or more measurements of same/similar 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
 - how much does one measurement type “explain” the other?
 - ICC: **same** measurement type – how reliable are the results?
 - Modeling frameworks: ANOVA, LME
 - 3 types of ICC: ICC(1,1), **ICC(2,1)**, **ICC(3,1)** – one-, two-way random- and mixed-effects ANOVA
 - Whole-brain voxel-level ICC
 - ICC(2,1): **3dLME -ICC** or **3dLME -ICCb**
 - 3dICC: ICC(1,1), ICC(2,1) and ICC(3,1)
- Chen et al. (2017), Human Brain Mapping 39(3) DOI:10.1002/hbm.23909

Naturalistic scanning

- Subjects view a natural scene during scanning
 - Visuoauditory movie clip (e.g., <http://studyforrest.org/>)
 - Music, speech, games, ...
- Duration: a few minutes (at least) or more
- Close to naturalistic settings: minimally manipulated
- Effect of interest: intersubject correlation (ISC) – 3dTcorrelate
 - Calculates correlation coefficient between voxel time series between subjects
 - Usual input is errts dataset after pre-processing to “correct” for motion, align to template space, et cetera
 - Extent of **synchronization** (“**entrainment**”)
 - Or of common response in that voxel/region across subjects to whatever they were experiencing
- Whole-brain voxel-wise group analysis of these voxel-wise inter-subject correlations: 3dISC

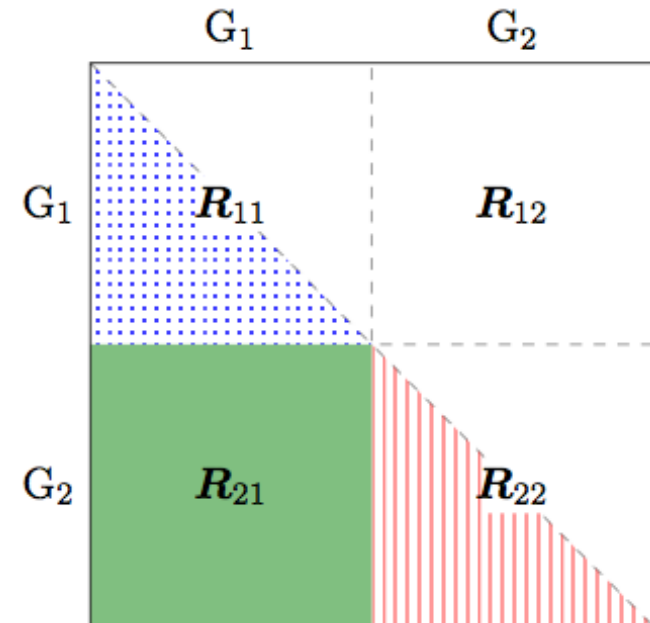
ISC group analysis

- Voxel-wise ISC matrix (usually Fisher/arctanh-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: R_{11} , R_{22}
 - Inter-group ISC: R_{21}
 - 3 group comparisons: R_{11} vs R_{22} , R_{11} vs R_{21} , R_{22} vs R_{21}



Complexity of ISC analysis

- 2 ISC values associated with a common subject are correlated with each other: 5 subjects $\rightarrow 5 \times 4 / 2 = 10$ ISC values
 - i.e., random fluctuations in inter-subject correlations are correlated ☹️
- $\rho \neq 0$ (unknown) characterizes non-independent relationship

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

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

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

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

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

Summary

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

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)
- **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)
- **3dICC** (intraclass correlation): prototype only
- **3dISC** (intersubject correlation): prototype only