Group Analysis

File: **afni24_GroupAna.pdf**

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SSCC/NIMH/NIH/DHHS/USA/Earth

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: (β_1, β_2, …, β_{20})=(1.13, 0.87, …, 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?
    - Subjects: random samples
    - Trials, regions?
  - Modeled as random variables: Gaussian distributions
  - Exchangeable, replaceable, generalizable

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

- Differentiations blurred under BML (Bayesian Multi-Level)

Terminology: main effects

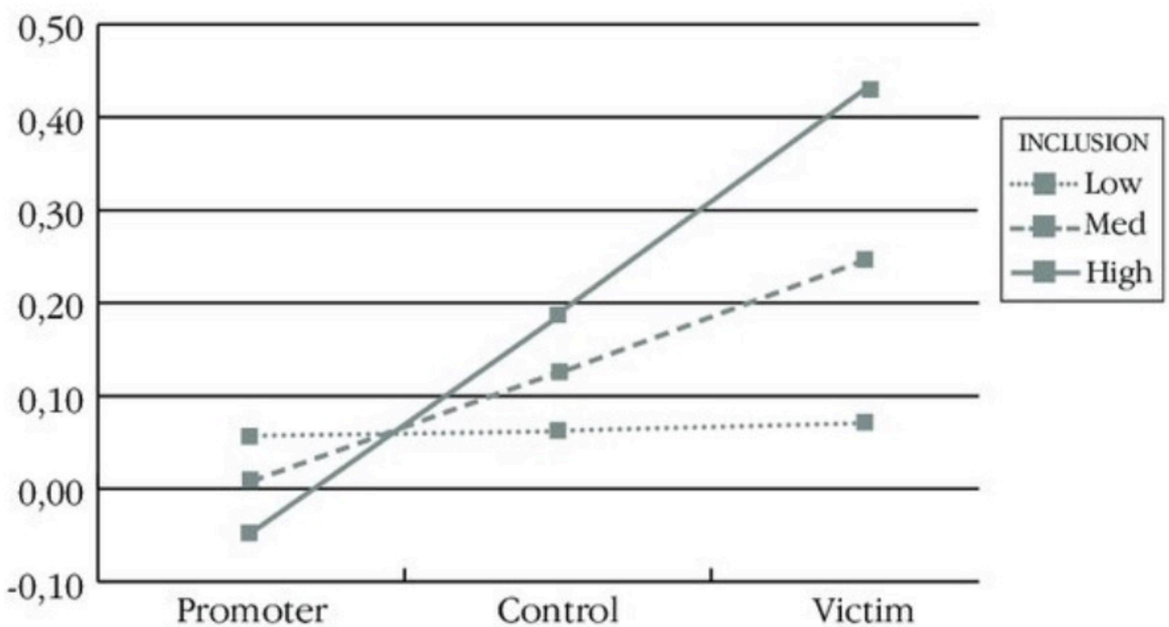
- Main effect for a fixed-effects factor
  - Omnibus: overall inference or summarization
    - e.g., Evidence for differences across 3 levels
    - Conventional ANOVA framework
    - *F*-statistic: not detailed enough
      - Tells you *something* is different, but not *which one*
    - Further partitions: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

      1) A > B, 2) A < B 3) A ≠ B

Terminology: interactions

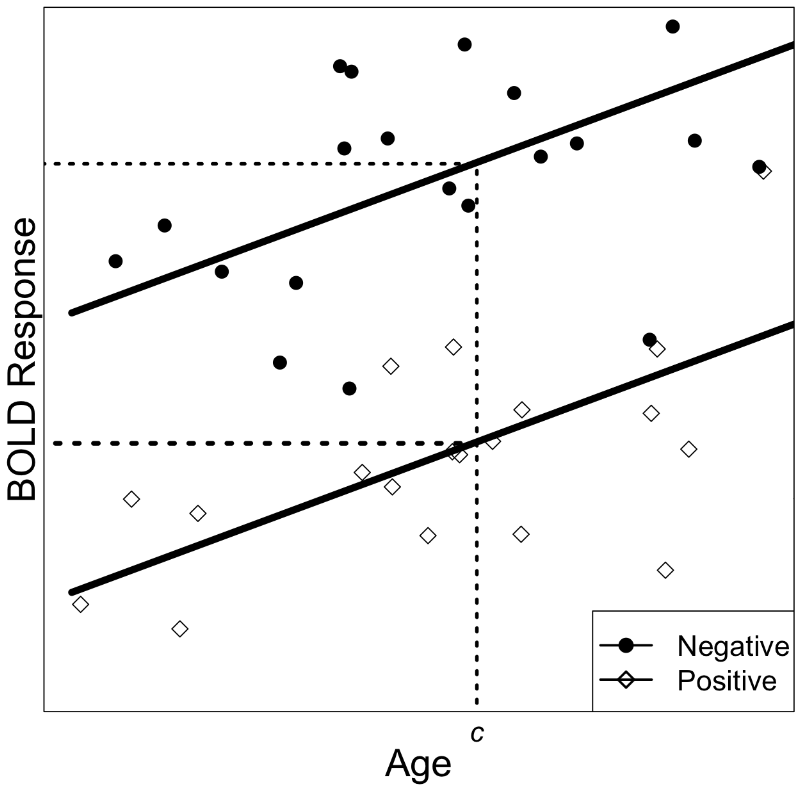
- Interaction effect between 2 or more factors
  - Omnibus: overall inference or summarization
    - Conventional ANOVA framework
    - *F*-statistic: not detailed enough to tell what specifically is happening
    - Further partitions: post hoc inferences via pairwise comparisons
  - 2 × 2 design: difference of difference
    - *F*-test for 2x2 interaction = *t*-test of

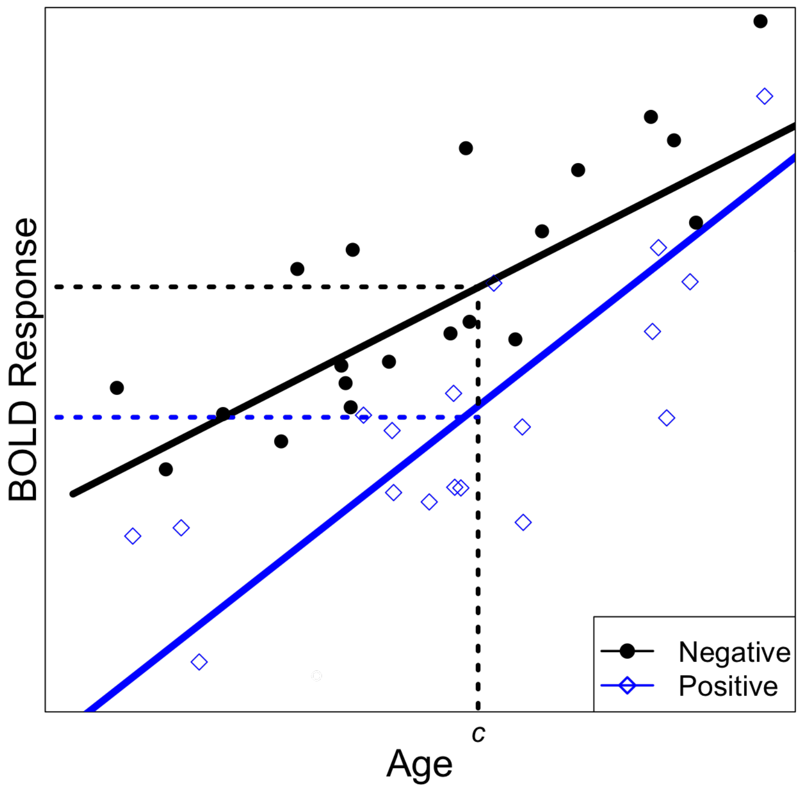
(A1B1 - A1B2) - (A2B1 - A2B2) or (A1B1 - A2B1) - (A1B2 - A2B2)



Terminology

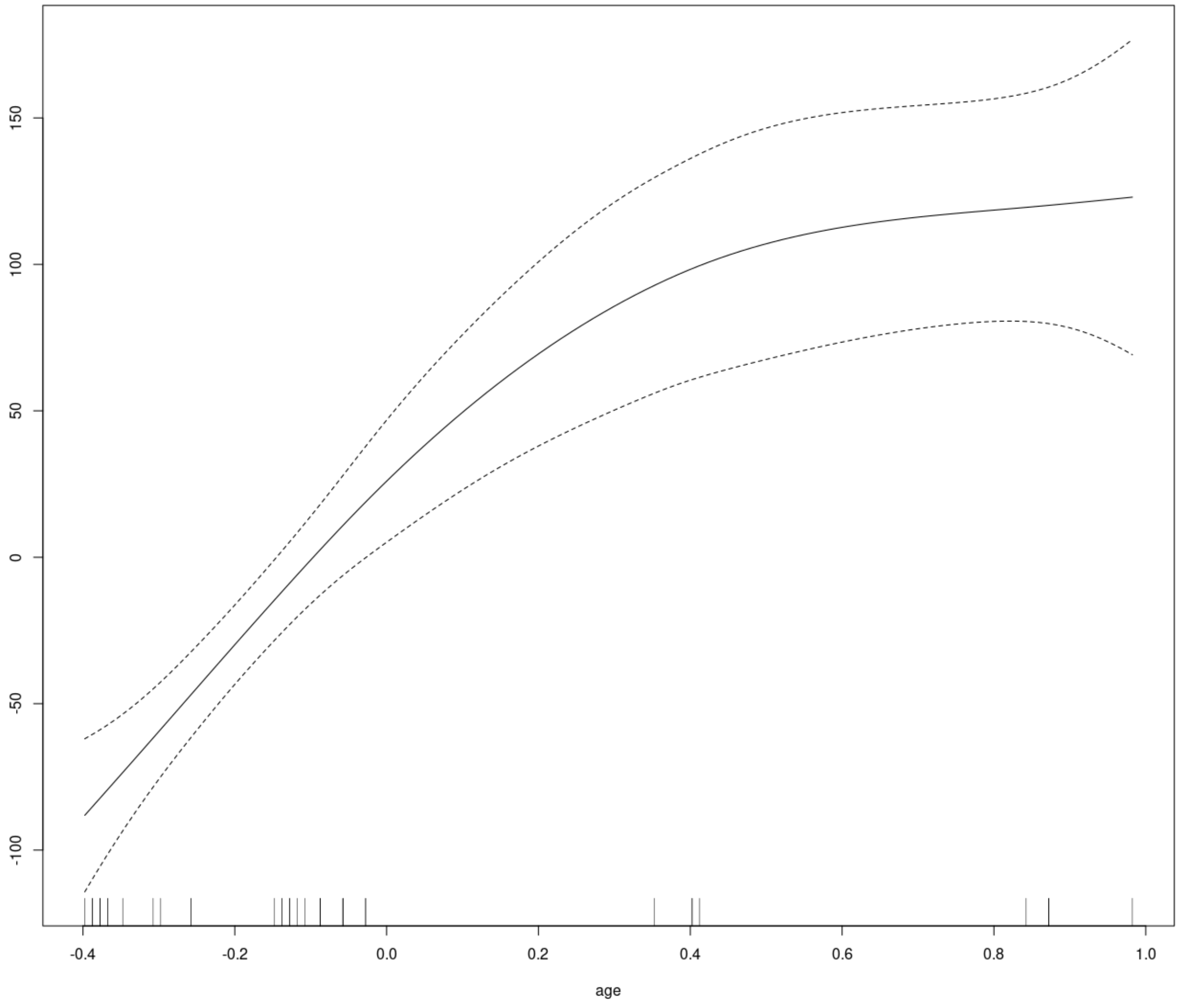
- Interaction effect involving a quantitative variable
  - By default: linearity (age, modulation, …)
    - Controlling: misconception – e.g., "covary out" age differences?
    - or, Effect of interest
  - Interaction between a factor and a quantitative variable





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

$$
\begin{array}{c} \text{Subj} \\ 1 \\ 1 \\ 1 \\ 2 \\ 2 \\ 2 \\ 3 \\ 3 \\ 3 \\ 4 \\ 4 \\ 4 \\ 5 \\ 5 \\ 5 \\ 6 \\ 6 \\ 6 \end{array}
\quad
\underbrace{\begin{pmatrix} \beta_{11} \\ \beta_{12} \\ \beta_{13} \\ \beta_{21} \\ \beta_{22} \\ \beta_{23} \\ \beta_{31} \\ \beta_{32} \\ \beta_{33} \\ \beta_{41} \\ \beta_{42} \\ \beta_{43} \\ \beta_{51} \\ \beta_{52} \\ \beta_{53} \\ \beta_{61} \\ \beta_{62} \\ \beta_{63} \end{pmatrix}}_{b}
=
\underbrace{\begin{pmatrix}
1 & 1 & 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\
1 & 1 & 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 \\
1 & 1 & -1 & -1 & -1 & -1 & 1 & 0 & 0 & 0 \\
1 & 1 & 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
1 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 0 \\
1 & 1 & -1 & -1 & -1 & -1 & 0 & 1 & 0 & 0 \\
1 & 1 & 1 & 0 & 1 & 0 & -1 & -1 & 0 & 0 \\
1 & 1 & 0 & 1 & 0 & 1 & -1 & -1 & 0 & 0 \\
1 & 1 & -1 & -1 & -1 & -1 & -1 & -1 & 0 & 0 \\
1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & 1 & 0 \\
1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & 1 & 0 \\
1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & 1 & 0 \\
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1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & 0 & 1 \\
1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & 0 & 1 \\
1 & -1 & 1 & 0 & -1 & 0 & 0 & 0 & -1 & -1 \\
1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & -1 & -1 \\
1 & -1 & -1 & -1 & 1 & 1 & 0 & 0 & -1 & -1
\end{pmatrix}}_{X \;(\text{columns } X_0, X_1, \ldots, X_9)}
\underbrace{\begin{pmatrix} \alpha_0 \\ \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \alpha_4 \\ \alpha_5 \\ \alpha_6 \\ \alpha_7 \\ \alpha_8 \\ \alpha_9 \end{pmatrix}}_{a}
+
\underbrace{\begin{pmatrix} \delta_{11} \\ \delta_{12} \\ \delta_{13} \\ \delta_{21} \\ \delta_{22} \\ \delta_{23} \\ \delta_{31} \\ \delta_{32} \\ \delta_{33} \\ \delta_{41} \\ \delta_{42} \\ \delta_{43} \\ \delta_{51} \\ \delta_{52} \\ \delta_{53} \\ \delta_{61} \\ \delta_{62} \\ \delta_{63} \end{pmatrix}}_{d}
$$

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

Correct:

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

Incorrect:

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

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

Correct

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

Incorrect

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

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

$$\mathbf{B}_{n\times m} = \mathbf{X}_{n\times q}\,\mathbf{A}_{q\times m} + \mathbf{D}_{n\times m}$$

Columns: B (Pos, Neg, Neu); X (Int, Grp, Age); A (Pos, Neg, Neu); D (Pos, Neg, Neu). Rows: Subj 1–6.

$$\begin{pmatrix} \beta_{11} & \beta_{12} & \beta_{13} \\ \beta_{21} & \beta_{22} & \beta_{23} \\ \beta_{31} & \beta_{32} & \beta_{33} \\ \beta_{41} & \beta_{42} & \beta_{43} \\ \beta_{51} & \beta_{52} & \beta_{53} \\ \beta_{61} & \beta_{62} & \beta_{63} \end{pmatrix} = \begin{pmatrix} 1 & 1 & -6 \\ 1 & 1 & 10 \\ 1 & 1 & 4 \\ 1 & -1 & -4 \\ 1 & -1 & -1 \\ 1 & -1 & -3 \end{pmatrix} \begin{pmatrix} \alpha_{01} & \alpha_{02} & \alpha_{03} \\ \alpha_{11} & \alpha_{12} & \alpha_{13} \\ \alpha_{21} & \alpha_{22} & \alpha_{23} \end{pmatrix} + \begin{pmatrix} \delta_{11} & \delta_{12} & \delta_{13} \\ \delta_{21} & \delta_{22} & \delta_{23} \\ \delta_{31} & \delta_{32} & \delta_{33} \\ \delta_{41} & \delta_{42} & \delta_{43} \\ \delta_{51} & \delta_{52} & \delta_{53} \\ \delta_{61} & \delta_{62} & \delta_{63} \end{pmatrix}$$

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 **`Pat`**ients (averaged across **`Cond`** values)

Improvement 1: precision information

- Conventional approach: βs 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 βs plus precision estimates
  - *t*-statistic contains precision ($t = \beta$ / SEM(β))
  - βs *and* their *t*-stats as input
  - βs 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

- **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 (among βs)
  - 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 βs per task/condition
  - More challenging: how to make inferences? H_0: $\beta_1=0$, $\beta_2=0$, …, $\beta_k=0$
- 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

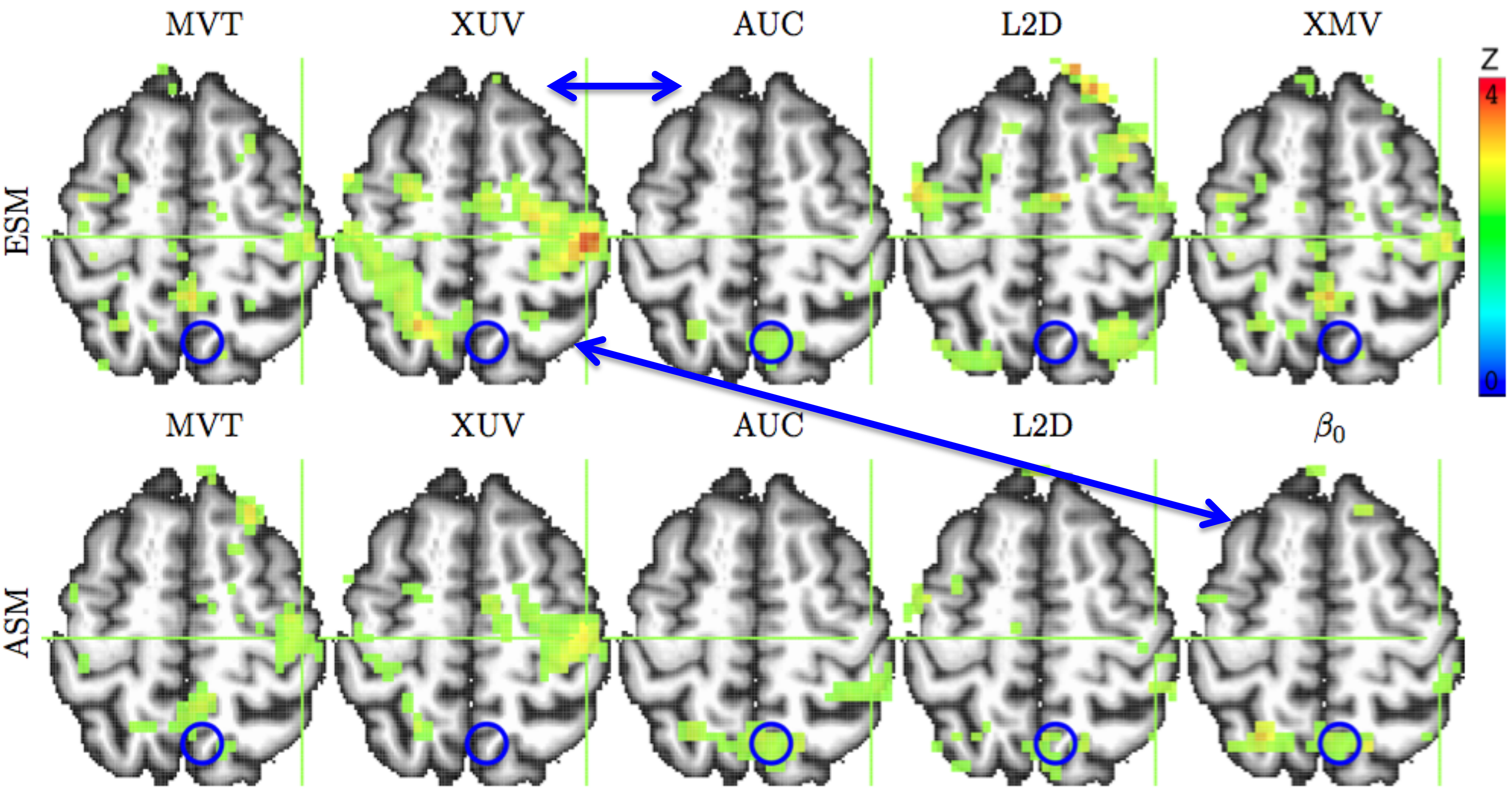
- Group analysis with HDR estimates: TENTzero, CSPLINzero
  - NHST: H_0: $\beta_1=0, \beta_2=0, \ldots, \beta_k=0$ [all responses in HRF = zero]
  - Area under curve (AUC) approach
    - Reduce HRF to one number: use area as magnitude approximation
    - Ignore **shape** subtleties
    - Shape information loss: (undershoot, peak location/width)
  - Better approach: maintaining shape integrity
    - Take individual $\boldsymbol{\beta}$s to group analysis (**M**VM)
    - One group with one condition: 3dLME
    - Other scenarios: treat βs 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

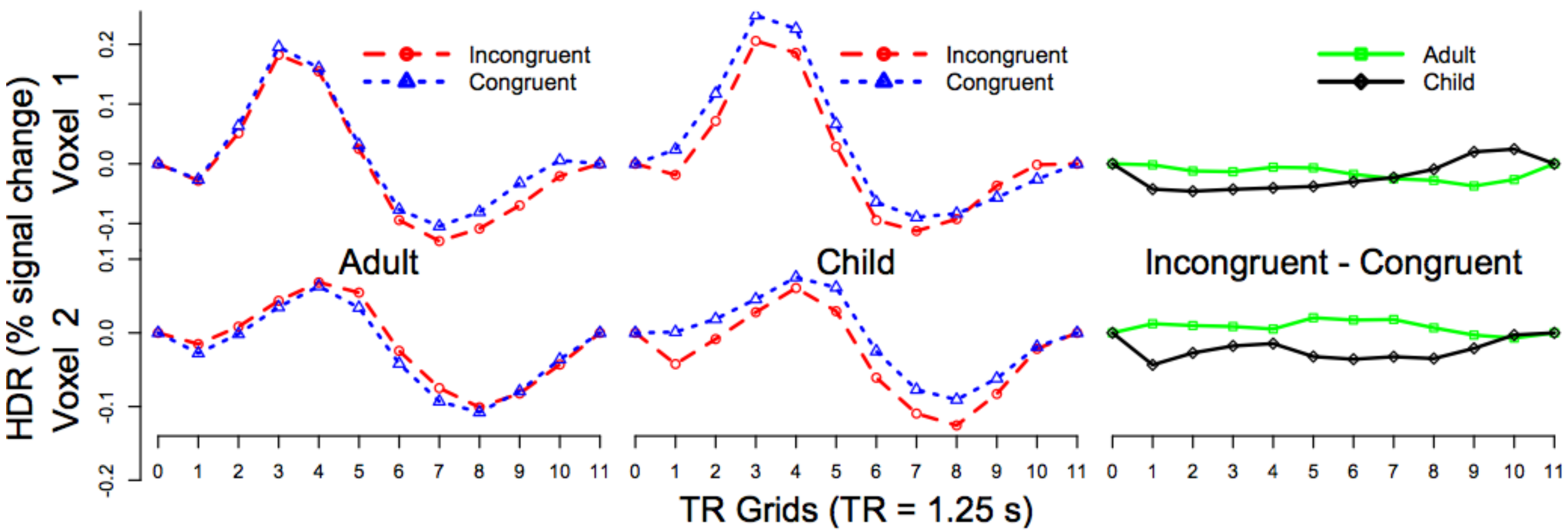
- 2 groups (children, adults), 2 conditions (congruent, incongruent), 1 quantitative covariate (age)
- 2 methods: HRF modeled by 10 (tents) and 3 (SPMG3) bases
- Effect of interaction: interaction group:condition – 3dMVM



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 significance testing: *p*-values)

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



Dealing with quantitative variables

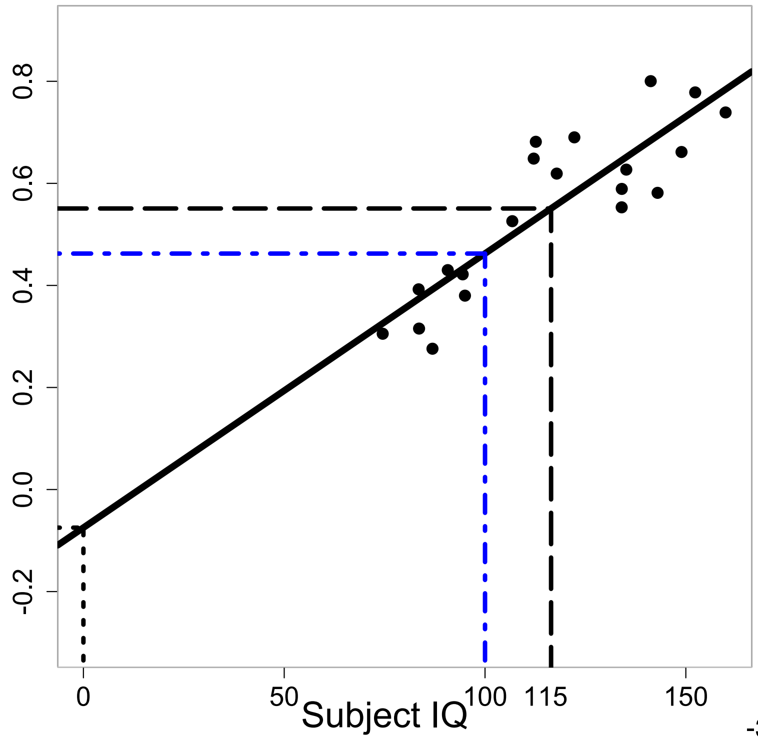
- Reasons to consider a covariate
  - Effect of interest: variability of response with some subject parameter
  - Model improvement: accounting for data variability with plausible cause
    - But you don't particularly care about this effect *per se*
- Frameworks
  - ANCOVA: between-subjects factor (e.g., 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

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

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

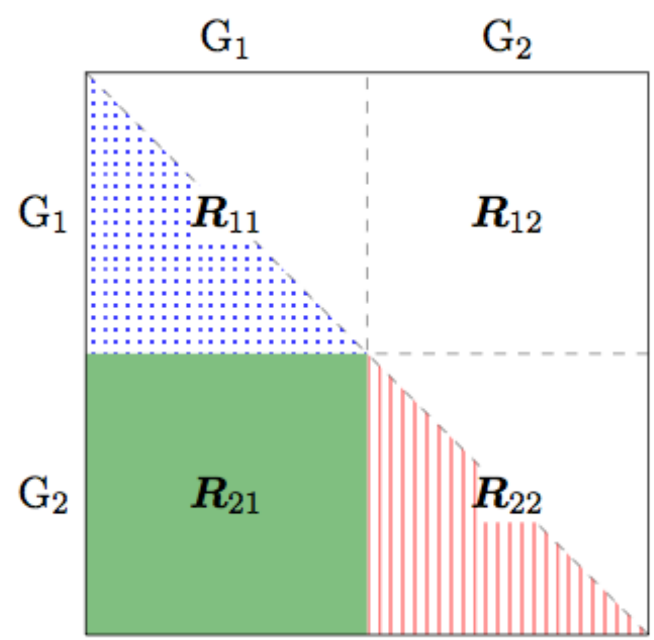
- Subjects view a natural scene during scanning
  - Visuoauditory movie clip (e.g., http://studyforrest.org/)
  - Music, speech, games, …
- Duration: a few minutes (at least) or more
- Close to naturalistic settings: minimally manipulated
- Effect of interest: intersubject correlation (ISC) – 3dTcorrelate
  - 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

$$\boldsymbol{R}^{(n)} = \begin{array}{c|ccccc} & S_1 & S_2 & S_3 & \cdots & S_n \\ \hline S_1 & 1 & r_{12} & r_{13} & \cdots & r_{1n} \\ S_2 & r_{21} & 1 & r_{23} & \cdots & r_{2n} \\ S_3 & r_{31} & r_{32} & 1 & \cdots & r_{3n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ S_n & r_{n1} & r_{n2} & r_{n3} & \cdots & 1 \end{array} \qquad \boldsymbol{Z}^{(n)} = \begin{array}{c|ccccc} & S_1 & S_2 & S_3 & \cdots & S_n \\ \hline S_1 & - & z_{12} & z_{13} & \cdots & z_{1n} \\ S_2 & z_{21} & - & z_{23} & \cdots & z_{2n} \\ S_3 & z_{31} & z_{32} & - & \cdots & z_{3n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ S_n & z_{n1} & z_{n2} & z_{n3} & \cdots & - \end{array}$$

- 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 ⇢ 5x4/2 = 10 ISC values
  - i.e., random fluctuations in inter-subject correlations are correlated ☹
- $\rho \neq 0$ (unknown) characterizes non-independent relationship

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

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

ISC: LME approach

- Modeling via effect partitioning: crossed random-effects LME

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

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

cross-subject

within-subject

- Charactering the relatedness among ISCs via LME

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

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

Chen et al, 2016. Untangling the Relatedness among Correlations, Part II: Inter-Subject Correlation Group Analysis through Linear Mixed-Effects Modeling. Neuroimage. NeuroImage 147:825-840

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

- **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