Group Analysis

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Overview

- Why do we need to do group analysis?
  - Summarizing results from multiple subjects
- Various group analysis approaches
  - *t*-tests: uber_ttest.py/3dttest++/3dttest, 3dMEMA
  - ANOVA-style: 3dANOVA/2/3, GroupAna
  - Advanced approaches: 3dLME
- Covariate modeling and complications
  - One group: uber_ttest.py/3dttest++, 3dMEMA, 3dLME
  - Two or more groups: : 3dttest++, 3dMEMA, 3dLME
- Nonparametric approach
- Fixed-effects analysis
- Miscellaneous

Summary: Individual Subject Analysis

- Basics of linear model
- FMRI experiment types
  - Block design; Event related experiment; Mixed
- FMRI data decomposition: three components
  - Baseline + slow drift + effects of no interest; Effects of interest; Unknown
  - Effects of interest: understanding BOLD vs. stimulus: IRF
- Modeling with fixed-shape IRF: GAM(*p*,*q*), BLOCK(*d*,*p*)
- Modeling with no assumption re: IRF (model free or data driven)
  - TENT(*b*,*c*,*n*), CSPLIN(*b*,*c*,*n*)
- Modeling with one major IRF plus shape adjustment
  - SPMG1/2/3
- Other issues
  - Multicollinearity
  - Catenation
  - Percent signal change

Individual Subject Analysis Comparison

			AFNI	**Others**
Baseline condition			Constant in linear model	Usually same as other conditions
Slow drift			Legendre polynomials (additive)	High-pass filtering and/or global mean scaling (multiplicative)
Effect comparison across subjects: Percent signal change			Voxel-wise scaling by temporal mean	1. Grand mean scaling 2. Special tools for % signal change
Serial correlation in residuals			Voxel-wise ARMA(1, 1)	Global AR(1) (SPM), Spatially regularized AR(1) (FSL)
Dealing with multiple runs	No catenation: analyze each run separately		Yes	FSL
	Catenation	Differentiate conditions across runs	Yes	SPM
		No differentiation for conditions across runs	Yes	----

Why Group Analysis?

- Summarizing individual subject results
- Why not one analysis with a mega model for all subjects?
  - Computationally unmanageable
  - Heterogeneity in data or experiment design across subjects
- What is a valid summarizing method?
  - Effect of subject *i* = group effect + deviation of subject *i*
    - A simple (one-sample *t*-test) model $\beta_i = b + \varepsilon_i$, $\varepsilon_i \sim N(0, \sigma^2)$
  - If individual effects are consistent across most or all subjects, the deviations would be relatively small
  - How small do we consider deviations comfortable?
    - Cross-subject variability measure: standard error
    - Significance measure = group effect relative to variability
      - Student *t*-test

Terminology: Fixed factor/effect - discrete variable

- Treated as a fixed variable (constant) in the model
  - Categorization of conditions/tasks (modality: visual/auditory)
    - Within-subject (repeated-measures) factor
  - Subject-grouping: Group of subjects (gender, normal/patients)
    - Between-subject factor
- All levels of a factor are of interest (house vs. face)
  - main effect, contrasts among levels
- Fixed in the sense of statistical inferences
  - apply only to the specific levels of the factor
  - don't extend to other potential levels that might have been included
- Fixed effects may also include continuous variables (covariates)
  - Of direct interest
  - Improving statistical power by controlling for data variability

- **Terminology**: Random factor/effect
  - Random variable in the model: exclusively subject in FMRI
    - average + effects uniquely attributable to each subject: *e.g.* $N(\mu, \tau^2)$
    - Requires enough number of subjects
  - Each individual subject effect 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
- Fixed vs. random effects
  - Conventional model $\beta_i = b + \varepsilon_i$, $\varepsilon_i \sim N(0, \sigma^2)$
  - Linear mixed-effects model $\beta_i = b + \delta_i + \varepsilon_i$, $\delta_i \sim N(0, \tau^2)$, $\varepsilon_i \sim N(0, \sigma^2)$
    - b: universal constant
    - δ_i: each subject's unique and consistent personality
    - ε_i: random fluctuations in life

Terminology: Covariate

- Historically a continuous variable: extension from *t*-test and ANOVAs
  - Factor (categorical) vs. covariate (continuous)
  - Examples: age, IQ, brain volume, personality measures, *etc*.
  - Modeling perspective
- Some people use it as effect of no interest
  - Effect of interest vs. effect of no interest
  - Could be discrete (gender, scanner, handedness) or continuous
  - User perspective
- First usage adopted here
  - Clarity, modeling consideration (more later)
  - In the end of the day it's the same model
  - A few caveats

Models at Group Level

- Conventional approach: taking $\boldsymbol{\beta}$ (or linear combination of multiple $\boldsymbol{\beta}$'s) only for group analysis
  - Assumption: all subjects have same precision (reliability, standard error, confidence interval) about $\boldsymbol{\beta}$
  - All subjects are treated equally
  - Student *t*-test: paired, one- and two-sample; ANOVA-style; LME
- Alternative: taking both $\boldsymbol{\beta}$ (or linear combination of multiple $\boldsymbol{\beta}$'s) and t-statistic
  - *t*-statistic contains precision information about $\boldsymbol{\beta}$
  - Each subject is weighted based on precision
  - Chen *et al*., FMRI Group Analysis Combining Effect Estimates and Their Variances. NeuroImage. 10.1016/j.neuroimage.2011.12.060
- All models are some sorts of linear model
  - *t*-test, ANOVA, LME, MEMA
  - Partition each subject's effect into multiple components

One-Sample Case

- One group of subjects ($n \geq 10$)
  - One condition (visual or auditory) effect
  - Linear combination of effects (visual - auditory)
- Null hypothesis H_0: average effect = 0
  - Rejecting H_0 is of interest!
- Results
  - Average effect at group level
    - Looks like nobody really cares about it ☹
  - Significance: *t*-statistic
    - Two-tailed by default (one-tailed: divide the sliderbar *p* by 2)
- Approaches
  - uber_ttest.py, 3dttest++ (3dttest), 3dMEMA

One-Sample Case: Example

- 3dttest++: taking β only for group analysis

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

- 3dMEMA: taking β and *t*-statistic for group analysis

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

Two-Sample Case

- Two groups of subjects ($n \geq 10$)
  - One condition (visual or auditory) effect
  - Linear combination of multiple effects (visual - auditory)
  - Example: Gender difference in emotion effect?
- Null hypothesis H_0: Group1 = Group2
  - Results
    - Group difference in average effect
    - Significance: *t*-statistic - Two-tailed by default
- Approaches
  - uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
  - One-way between-subjects ANOVA
    - 3dANOVA: can also obtain individual group test

Paired Case

- One groups of subjects ($n \geq 10$)
  - Two conditions (visual or auditory): no missing data allowed
  - Example: House vs. Face; Visual vs. Auditory
- Null hypothesis H_0: Condition1 = Condition2
  - Results
    - Average effect at group level
    - Significance: *t*-statistic (Two-tailed by default)
- Approaches
  - uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
  - One-way within-subject (repeated-meaures) ANOVA
    - 3dANOVA2 –type 3: can also obtain individual condition test
- Essentially equivalent to one-sample case
  - Use contrast instead of individual effects as input

Paired Case: Example

- 3dttest++: comparing two conditions

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

Paired Case: Example

- 3dMEMA: comparing two conditions

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

One-Way Between-Subjects ANOVA

- Two or more groups of subjects ($n \geq 10$)
  - One condition or linear combination of multiple conditions
  - Example: House, face, or house vs. face
- Null hypothesis H_0: Group1 = Group2
  - Results
    - Average group difference
    - Significance: *t*- and F-statistic (two-tailed by default)
- Approaches
  - 3dANOVA
  - With more than two groups, can break into pairwise group comparisons with 3dttest++ (3dttest), 3dMEMA

Multiple-Way Between-Subjects ANOVA

- Two or more subject-grouping factors: factorial
  - One condition or linear combination of multiple conditions
  - Example: gender, control/patient, genotype, handedness, …
- Testing main effects, interactions, single group, group comparisons
  - Significance: *t*- (two-tailed by default) and F-statistic
- Approaches
  - Factorial design (imbalance not allowed): two-way (3dANOVA2 –type 1), three-way (3dANOVA3 –type 1)
  - Up to four-way ANOVA: GroupAna (imbalance allowed)
  - All factors have two levels: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
  - Using group coding with 3dttest++ (3dttest), 3dMEMA: imbalance allowed

One-Way Within-Subject ANOVA

- Also called one-way repeated-measures: one group of subject ($n \geq 10$)
  - Two or more conditions
  - Example: happy, sad, neutral
- Main effect, simple effects, contrasts and general linear tests
  - Significance: *t*- (two-tailed by default) and *F*-statistic
- Approaches
  - 3dANOVA2 -type 3 (two-way ANOVA with one random factor)
  - With two conditions, equivalent to paired case with 3dttest++ (3dttest), 3dMEMA
  - With more than two conditions, can break into pairwise comparisons with 3dttest++ (3dttest), 3dMEMA

One-Way Within-Subject ANOVA

- Example: visual vs. auditory condition

```
3dANOVA2 -type 3 -alevels 2 -blevels 10           \
 -prefix Vis_Aud -mask mask+tlrc                  \
  -dset 1 1  'OLSQ.FP.b+tlrc[Vrel#0_Coef]'        \
  -dset 1 2  'OLSQ.FR.b+tlrc[Vrel#0_Coef]'        \
        ……
  -dset 1 10 'OLSQ.GM.b+tlrc[Vrel#0_Coef]'        \
  -dset 2 1  'OLSQ.FP.b+tlrc[Arel#0_Coef]'        \
  -dset 2 2  'OLSQ.FR.b+tlrc[Arel#0_Coef]'        \
        ……
  -dset 2 10 'OLSQ.GM.b+tlrc[Arel#0_Coef]'        \
  -amean 1 V                                      \
  -amean 2 A                                      \
  -adiff 1 2 VvsA                                 \
  -fa FullEffect                                  \
  -bucket anova.VA
```

Two-Way Within-Subject ANOVA

- Factorial design; also known as two-way repeated-measures
  - Two within-subject factors
  - Example: emotion and category (visual/auditory)
- Testing main effects, interactions, simple effects, contrasts
  - Significance: *t*- (two-tailed by default) and F-statistic
- Approaches
  - 3dANOVA3 –type 4 (three-way ANOVA with one random factor)
  - All factors have two levels: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
  - Missing data?
    - Break into t-tests: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
    - 3dLME (work in progress)

Two-Way Mixed ANOVA

- Factorial design
  - One between-subjects and one within-subject factor
  - Example: gender (male and female) and emotion (happy, sad, neutral)
- Testing main effects, interactions, simple effects, contrasts
  - Significance: *t*- (two-tailed by default) and F-statistic
- Approaches
  - 3dANOVA4 –type 5 (three-way ANOVA with one random factor)
  - If all factors have two levels, can run 3dttest++ (3dttest), 3dMEMA
  - Missing data?
    - Unequal number of subjects across groups: GroupAna
    - Break into t-test: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
    - 3dLME (work in progress)

Group analysis with multiple basis functions

- Basis functions: TENT, CSPLIN
  - Area under the curve (AUC) approach
    - Forget about the subtle shape difference
    - Focus on the response magnitude measured by AUC
    - Issues: Shape information lost; Undershoot may cause trouble
  - Maintaining shape information
    - Null hypothesis H_0: $\beta_1=\beta_2=\ldots=\beta_k=0$ (NOT $\beta_1=\beta_2=\ldots=\beta_k$)
    - 3dLME: can only handle simple cases, not sohisticated ANOVA
    - Result: F-statistic for H_0 and t-statistic for each basis function
    - Limitation: only works for simple cases and is difficult to handle ANOVA-style analysis
- Basis functions of SPMG2/3: Only take SPMG1 to group

A few cases where 3dLME shines

- Maintaining shape information with TENT/CSPLIN
- Multiple effect estimates (runs/sessions) per conditions
  - Number of effect estimates may vary across conditions and subjects
- Covariate modeling at the presence of within-subject (or repeated-measures) variable
- Subject-specific random effect in covariate modeling
- Missing data in longitudinal studies
  - Missing at random (MAR)
- Group studies involving family members or twins
  - Subjects are genetically related within each family
  - Specify variance-covariance structure for genetic relatedness

If your case hasn't been covered so far

- GroupAna (up to four-way ANOVA)
- If all factors have two levels, run 3dttest++ (3dttest), 3dMEMA
- Try to break into multiple t-tests: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
- 3dLME (work in progress)
- Still can't find a solution?
  - Blame YOURSELF! Should have thought of the situation in experiment design
  - Let me know

Covariates

- Confusing usage in literature
  - May or may not be of direct interest
    - Direct interest: relation between response and the covariate
      - Is response proportional to response time?
    - Of no interest: confounding, nuisance, or interacting variables
      - Controlling for or covarying or partialling out: what does it mean?
      - Subtle issue in this case: centering
  - Continuous or discrete
    - Continuous: historically originated from ANCOVA
    - I solely use it as a continuous variable to avoid confusion
    - Very careful when treating a discrete (categorical) variable as covariate
      - Dummy coding
      - Interaction

Covariate: Modeling framework

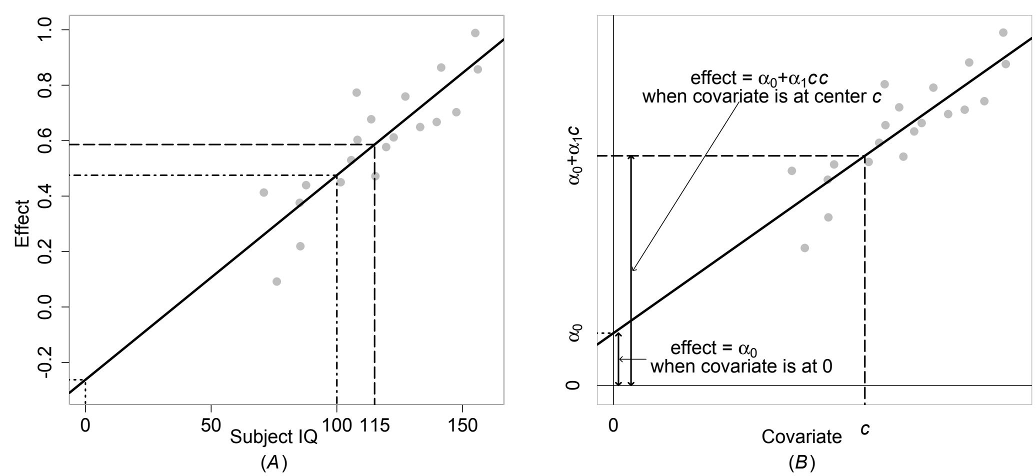
- Most people learned covariate modeling with ANCOVA
  - Historical extension to ANOVA
  - Quite limited and not flexible
  - Not a good approach in general
- GLM or LME: broader context
  - All explanatory variables are treated equally in the model
  - Doesn't matter: variable of interest or not, discrete or continuous
  - Discrimination or categorization occurs only at human (not model) level

What variables can serve as covariate?

- Considerations
  - Subject-level (vs. trial-level: handled via amplitude modulation)
  - Usually one value per subject, but maybe more than one with within-subject factor
  - Tons of potential candidates: Overfitting
  - Prior information
  - Outlier information from 3dMEMA
- Examples
  - Age, IQ, brain volume, cortex thickness
  - Behavioral data: reaction time
    - Amplitude modulation deals with cross-trial variability at individual level
    - Covariate modeling at group level handles variability across subjects

Handling covariates: one group

- Model $y_i = \alpha_0 + \alpha_1 x_i + \varepsilon_i$, for ith subject: no other variables
  - α_1 - slope (change rate, marginal effect): effect per unit of x
    - Simple and straightforward: no manipulation needed
  - α_0 – intercept (x=0): group effect while controlling x
    - Controlling is NOT good enough
    - Interpretability - α_0 at what x value: mean or any other value?
    - Centering is crucial for interpretability
      - Center does not have to be mean



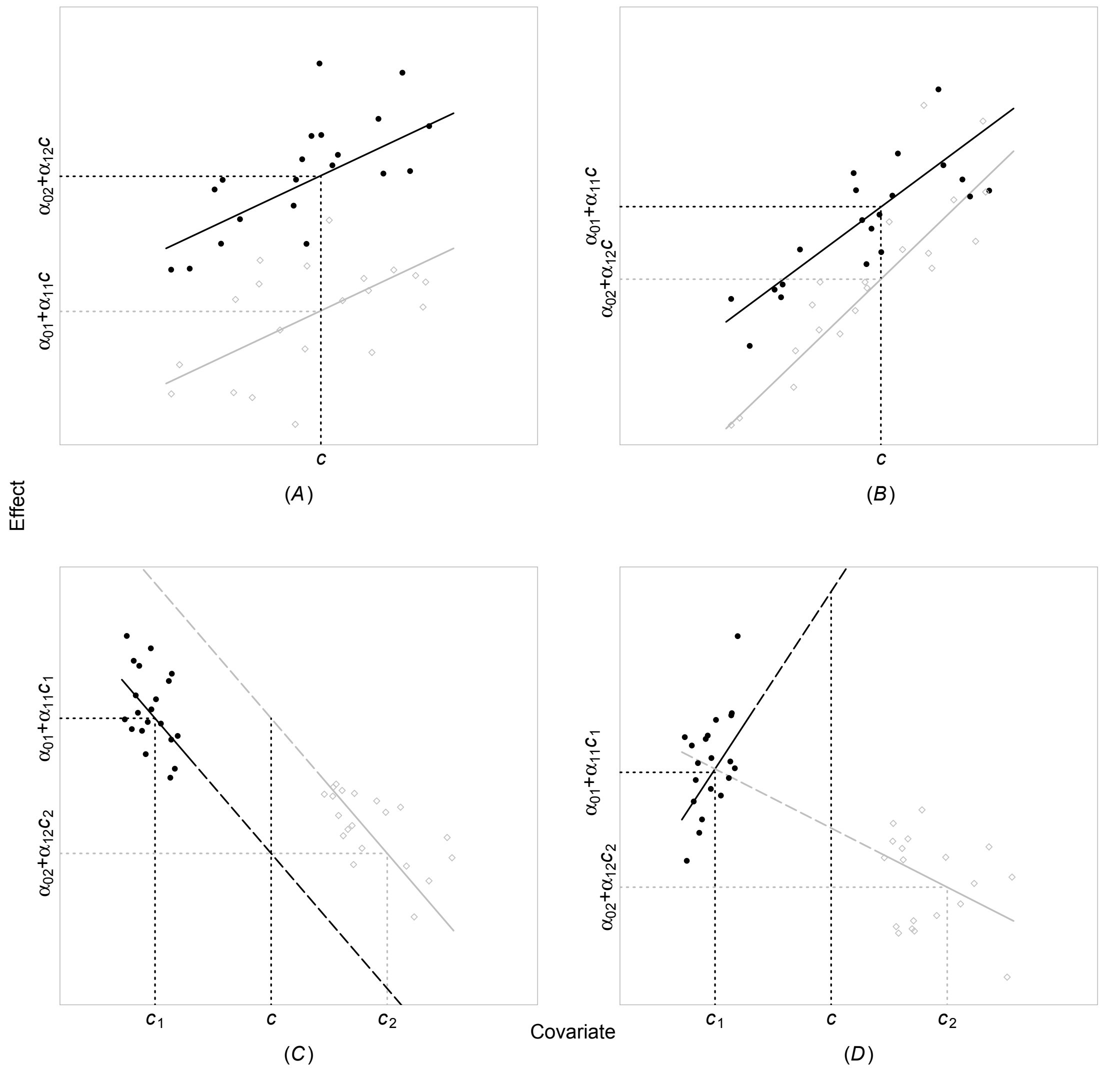
Covariates: two or more groups

- Slope
  - Same or different across groups?
  - Usually we don’t know in advance
    - Start with different slopes – interaction between group and covariate
    - If same, then model tuning
- Intercept: centering again
  - Same or different center across groups?
  - How to decide? Plot out covariate distribution
  - If about the same, nice and easy!
  - If dramatically different, now what?
  - If possible, this issue should have been though of when designing the experiment
    - You may balance covariate values (e.g. age) across groups
    - How about if it is not under your control (e.g., response time)?

Covariates: different center across groups

- Most statisticians (including in FMRI) consider it **horrible**
  - For example, Miller GM and Chapman JP. '*Misunderstanding analysis of covariance*', J Abnormal Psych 110: 40-48 (2001)
  - SPM and FSL communities
  - It may well be the case
    - Groups were not balanced in experiment design: design failure!
    - E.g., males and females have different age distribution, and we can't resolve: in the end the group difference is due to sex or age difference?
  - But I beg to differ under other scenarios
    - Now stop and think!
    - What is the point of considering the covariate? Using RT as example, we can account for within-group variability of RT, not variability across all subjects in both groups
    - Strategy: Centering differently across groups!
      - Do NOT center around a common point: overall mean, for exampl
      - Age: adolescents vs. seniors: what would it happen when centering around

Slope and intercept with two groups



Treating Categorical Variable as Covariate

- Popular coding methods
  - Dummy coding: 0s and 1s with a reference (or base) level (group)

$$x_{ij} = \begin{cases} 1, & i\text{th subject at } j\text{th level, and } j \neq k \\ 0, & \text{otherwise} \end{cases}$$

    - Convenient for group difference
  - Cell mean coding: 0s and 1s without intercept

$$x_{ij} = \begin{cases} 1, & i\text{th subject is at } j\text{th level} \\ 0, & \text{otherwise} \end{cases}$$

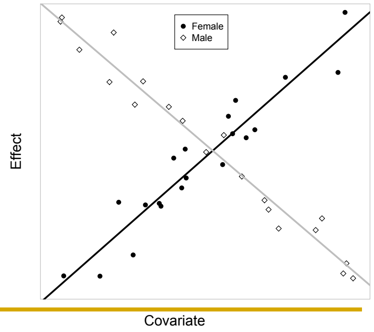
    - Good for individual group effect
  - Effect (or deviation) coding: 1, 0, and -1 with a reference (or base) level (group)

$$x_{ij} = \begin{cases} 1, & i\text{th subject at } j\text{th level, and } j \neq k \\ 0, & i\text{th subject not at } j\text{th level, and } j \neq k \\ -1, & i\text{th subject at } k\text{th level} \end{cases}$$

    - Nice for main effect across groups

Caveats: Categorical Variable as Covariate

- Most people simply add a categorical variable in the model as an additive explanatory variable
  - For example, male/female, scanners, …
  - Most people don't even look into group difference, but it might be of scientific interest in the first place; even if not so, such difference warrants discussion instead of sweeping under the carpet
  - Centering? Depending on specific coding strategy! Effect coding is preferable with two groups, and centering is not needed especially the 2 groups have unequal number of subjects
  - With other variables present, it could be problematic without considering interactions between grouping and other variables
- Coding is usually done internally in 3dttest++/3dMEMA
  - Option available for interaction
  - With > 1 grouping variable, coding may be needed



Covariate Modeling: Sophisticated Cases

- With presence of within-subject factor
  - Most statisticians think (including in FMRI) should NOT be done: cross-level difference may be correlated with the covariate, thus invalidating the purpose of incorporating the covariate
  - I tend to disagree again: same as cross-group scenario
    - Check covariate distribution across levels
    - Similar mean: overall centering
    - Different mean: disparate centering allows for accounting for within-level variability
    - Program: 3dLME (work in progress)
- Cross-subject adjustment in covariate modeling
  - Each subject may have different slope
  - Program: 3dLME

• Group Analysis: Non-Parametric Approach

- Parametric approach
  - Enough number of subjects> $n \geq 10$
  - Random effects of subjects: usually Gaussian distribution
  - Individual and group analyses: separate

- Non-parametric approach
  - Moderate number of subjects: $4 < n < 10$
  - No assumption of data distribution (e.g., normality)
  - Statistics based on ranking or permutation
  - Individual and group analyses: separate

• Group Analysis: Fixed-Effects Analysis

- When to consider?
  - Group level: a few subjects: $n < 6$
  - Individual level: combining multiple runs/sessions
- Case study: difficult to generalize to whole population
- Model $\beta_i = b+\varepsilon_i$, $\varepsilon_i \sim N(0, \sigma_i^2)$, σ_i^2: within-subject variability
  - Fixed in the sense that cross-subject variability is not considered
- Direct fixed-effects analysis (**3dDeconvolve/3dREMLfit**)
  - Combine data from all subjects and then run regression
- Fixed-effects meta-analysis (**3dcalc**) : weighted least squares
  - $\beta = \sum w_i\beta_i/\sum w_i$, $w_i = t_i/\beta_i$ = weight for ith subject
  - $t = \beta\sqrt{\sum w_i}$

• 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-effects factor
    - Can't handle covariates

• Miscellaneous

- Missing data: missing at random (MAR)
  - Remove subjects from analysis
  - Can't afford to exclude subjects: 3dLME
- Voxelwise covariate: 3dttest++
- Compare to a constant
  - Null hypothesis H_0: response = 1%; 3dttest -base1 bval
- Compare to a voxelwise constant (*e.g.*, one patient)
  - 3dttest -base1_dset DSET
- Correlation between two sets of 3D data: two conditions, one correlates with the other?
  - 3ddot –demean
  - 3dttest++: 3dMean -> mean, 3dMean –sd -> SD, and then 3dcalc to standardize
- Post hoc ROI analysis
  - May not be consistent with voxelwise results

Group Analysis Program List

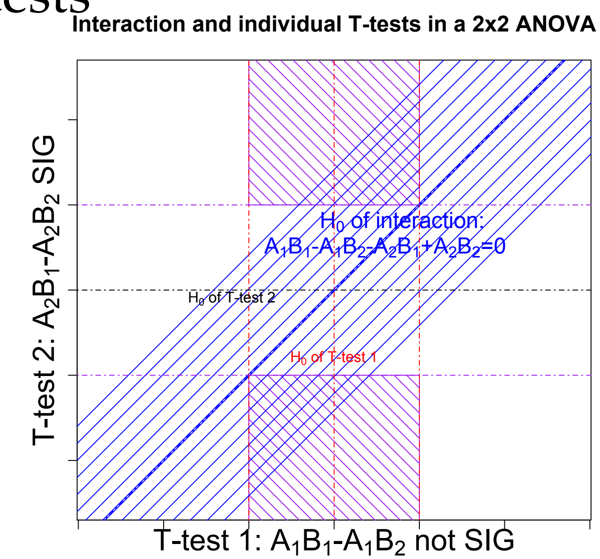
- **3dttest++** (one-sample, two-sample and paired *t*) + covariates (voxel-wise)
  - **3dttest is almost obsolete except for two special cases**
- **3dMEMA** (R package for mixed-effects analysis, t-tests plus covariates)
- **3dttest** (mostly obsolete: one-sample, two-sample and paired *t*)
- **3ddot** (correlation between two sets)
- **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** (obsolete: regression/correlation, covariates)
- **GroupAna** (Matlab package for up to 5-way ANOVA)
- **3dLME** (R package for various kinds of group analysis)

• Two perspectives: batch vs. piecemeal

- ANOVA: factors/levels, balancedness
  - Main effects, interactions, simple effects, contrasts, …
  - **Syntactic sugar** for a special subgroup of LME
  - Almost everybody trained in the conventional paradigm
  - Institutionalized; stuck in a rut
  - Pros: get almost everything you want in one batch model
  - Cons: *F*-stat for main effect or 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…**), and with assumptions: homogeneity with multiple groups, and compound symmetry when a within-subject factor has more than 2 levels
- Tests of interest
  - Simple/straightforward/piecemeal: focus on each test & handle one at a time
  - Mainly *t*-stat: one-sample, paired, two-sample
  - All main effects and interactions can be teased apart into multiple *t*-tests
  - No stringent assumptions such as compound symmetry

• Teasing apart *F*-statistic

- *F* for the main effect of a factor with two levels is essentially *t*
  - ➢ *F* carries less information than *t*: directionality
- *F* for interactions of all factors with two levels are essentially *t*
  - ➢ *F*-test for interaction between A and B: equivalent to *t*-test for (A1B1-A1B2)-(A2B1-A2B2) or (A1B1-A2B1)-(A1B2-A2B2), but *t* is better than *F*: a positive *t* shows A1B1-A1B2 > A2B1-A2B2 and A1B1-A2B1 > A1B2-A2B2
  - ➢ Again *F* carries less information than *t*: directionality
- With > 2 levels, *F*-statistic corresponds to multiple *t*-tests
  - ➢ *F* not significant, but some individual *t*-tests significant; or the other way around



FMRI Group Analysis Comparison

<table>
<tr><th colspan="2"></th><th>AFNI</th><th>SPM</th><th>FSL</th></tr>
<tr><td colspan="2">t-test (one-, two-sample, paired)</td><td>3dttest++, 3dMEMA</td><td>Yes</td><td>FLAME1, FLAME1+2</td></tr>
<tr><td colspan="2">One categorical variable: one-way ANOVA</td><td>3dANOVA/2/3, GroupAna</td><td>Only one categorical variable: flexible and full factorial design</td><td>Only one categorical variable: FLAME1, FLAME1+2</td></tr>
<tr><td colspan="2">More than one categorical variables: multi-way ANOVA</td><td>3dANOVA2/3, GroupAna, 3dLME</td><td>---</td><td>---</td></tr>
<tr><td colspan="2">Subject-specific covariate + one or more subject-grouping variables</td><td>3dttest++ (voxel-wise covariate possible), 3dMEMA</td><td>Yes</td><td>FLAME1, FLAME1+2</td></tr>
<tr><td rowspan="4">Sophisticated situations</td><td>Covariate + within-subject factor</td><td rowspan="4">3dLME</td><td rowspan="4">---</td><td rowspan="4">---</td></tr>
<tr><td>Subject adjustment in trend analysis</td></tr>
<tr><td>Basis functions</td></tr>
<tr><td>Missing data</td></tr>
</table>

Summary

- Why do we need to do group analysis?
  - Summarizing results from multiple subjects
- Various group analysis approaches
  - *t*-tests: uber_ttest.py/3dttest++/3dttest, 3dMEMA
  - ANOVA-style: 3dANOVA/2/3, GroupAna
  - Advanced approaches: 3dLME
- Covariate modeling and complications
  - One group: uber_ttest.py/3dttest++, 3dMEMA, 3dLME
  - Two or more groups: : 3dttest++, 3dMEMA, 3dLME
- Nonparametric approach
- Fixed-effects analysis
- Miscellaneous