Handling Relatedness among Subjects through Linear Mixed-Effects Modeling in Neuroimaging

Poster #: 623

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Relatedness among subjects

Subjects from large studies (e.g., ABCD)

- Some subjects are from same families
  - Siblings, monozygotic or dizygotic twins, triplets, half siblings, cousins
  - Parent-child
- How to accurately characterize the relatedness in the population-level model?

Model formulation

- Effect decomposition through linear mixed-effects model
- Relatedness captured through a two-level structure
  - Families
  - Subjects within each family

Demo dataset

Data structure: 3 groups

- Group 1 (controls with no relatives): n_1=32, age 50.2±11.0 years, 20 F/12 M
- Group 2 (patients): n_2=21, age 56.2±15.8 years, 19 F/2 M
- Group 3 (controls with relatives in Group 2): n_3=21, 48.6±16.2 years; 17 F/4 M

Relatedness

- Each subject in group 2: genetically related to one in group 3
- Relationship: 10 parent-child, 7 full siblings, 3 cousins, 1 great nephew

Model construction

LME formulation (Bates et al., 2015)

$$y_{ij} = \boldsymbol{x}_{ij}^T \boldsymbol{a} + z_{0j} + z_{1j} u_{ij} + \varepsilon_{ij}$$

- y_{ij}: effect of subject *i* in family *j*
- $\boldsymbol{x}_{ij}$: subject-level covariates (e.g., group, sex, age)
- $\boldsymbol{a}$: effects associated with the covariates $\boldsymbol{x}_{ij}$
- z_{0j}: effect for family *j*
- z_{1j}: relatedness effect with family *j*
- u_{ij}: relatedness indicator
- ε_{ij}: residual associated subject *i* in family *j*

Assumptions

- Linearity
- Gaussianity: $z_{0j} \sim N(0, \tau_0^2), z_{1j} \sim N(0, \tau_1^2),\ \varepsilon_{ij} \sim N(0, \sigma^2)$

References

Bates, D., Maechler, M., Bolker, B., Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software, 67(1):1-48.

Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S., Cox, R.W. (2013). Linear Mixed-Effects Modeling Approach to FMRI Group Analysis. NeuroImage 73:176-190.

Solving LME model

Whole-brain voxel-wise analysis

- Program available in AFNI: `3dLMEr` (Chen et al., 2013)
- Implementation using R package lme4 (Bates et al., 2015)
- Shell scripting interface
- Flexibility in specifying various random-effects structures
- Main effects, interactions and effect comparisons
- Runtime with demo dataset: 40 min (16 CPUs)

Characterization of relatedness

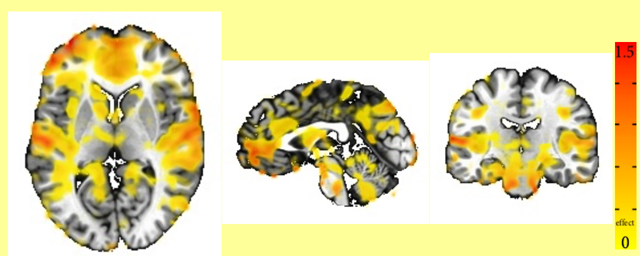
- Intraclass correlation
- Extent of similarity between two members in the same family

$$\text{ICC} = \frac{\tau_0^2 + \tau_1^2}{\tau_0^2 + \tau_1^2 + \sigma^2}$$

Results

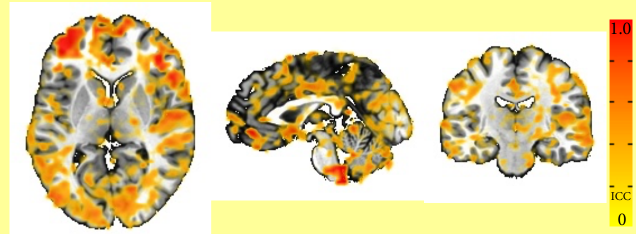
Comparison: Group 2 (patients) vs Group 1 (controls with no relatives)

- Effects shown instead of statistical evidence as typically practiced
- Full results shown without artificial and arbitrary thresholding
- Avoiding illusionary dichotomization of "truth" and "falsehood"



Relatedness in the brain: ICC

- Extent of effect similarity between Group 2 and Group 3



Program available in AFNI: `3dLMEr`

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