Naturalistic FMRI:

How to Run Inter-Subject Correlation Group Analysis?

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Introduction: Naturalistic FMRI paradigm

✧ Naturalistic scanning

- Subjects view a natural scene (e.g., movie clip) during most of or the entire scanning session [1]
- **Effect of interest**: extent of synchronization, similarity, or shared processing **at the same locations** in the brain among subjects
  - Inter-Subject Correlation (**ISC**): correlation of time series between two subjects *at the same location in the brain*

✧ Comparisons with conventional methods

Typical task-related experiments

- Meticulously designed, well controlled
- Duration of each task/condition: usually 20s or less
- **Effect of interest**: regional response to a task/condition
- Response size directly modeled through temporal regression
- Summarized through group analysis (*t*-tests, GLM, AN(C)OVA, LME)

Resting-state

- No explicit task
- **Effect of interest**: regional correlation, networks (e.g., DMN)
- Modeled through seed-based correlation, data-driven methods, etc.

✧ **Challenge:** How to perform ISC group analysis?

Characteristics of ISC data

- One group: focus on lower triangular part due to matrix symmetry

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

- **Relatedness**: 10 ISC values from 5 subjects (5×4/2 pairs)
  - Some components are correlated: $0 \le \rho \le 0.5$ characterizes non-independent relationship ("correlations of the correlations")
  - **How to handle this special structure in ISC group analysis?**

$$\boldsymbol{P}^{(5)} = \begin{array}{c} \\ z_{21} \\ z_{31} \\ z_{41} \\ z_{51} \\ z_{32} \\ z_{42} \\ z_{52} \\ z_{43} \\ z_{53} \\ z_{54} \end{array} \begin{array}{c} \begin{array}{cccccccccc} z_{21} & z_{31} & z_{41} & z_{51} & z_{32} & z_{42} & z_{52} & z_{43} & z_{53} & z_{54} \end{array} \\ \begin{pmatrix} 1 & \rho & \rho & \rho & \rho & \rho & \rho & 0 & 0 & 0 \\ \rho & 1 & \rho & \rho & \rho & 0 & 0 & \rho & \rho & 0 \\ \rho & \rho & 1 & \rho & 0 & \rho & 0 & \rho & 0 & \rho \\ \rho & \rho & \rho & 1 & 0 & 0 & \rho & 0 & \rho & \rho \\ \rho & \rho & 0 & 0 & 1 & \rho & \rho & \rho & \rho & 0 \\ \rho & 0 & \rho & 0 & \rho & 1 & \rho & \rho & 0 & \rho \\ \rho & 0 & 0 & \rho & \rho & \rho & 1 & 0 & \rho & \rho \\ 0 & \rho & \rho & 0 & \rho & \rho & 0 & 1 & \rho & \rho \\ 0 & \rho & 0 & \rho & \rho & 0 & \rho & \rho & 1 & \rho \\ 0 & 0 & \rho & \rho & 0 & \rho & \rho & \rho & \rho & 1 \end{pmatrix} \end{array}$$

Previous approaches: never validated before

- Student's *t*-test: correlation structure not properly handled
- Nonparametric methods: various types of permutations, e.g., randomizing time series across voxels and time points (ISC Toolbox [2])

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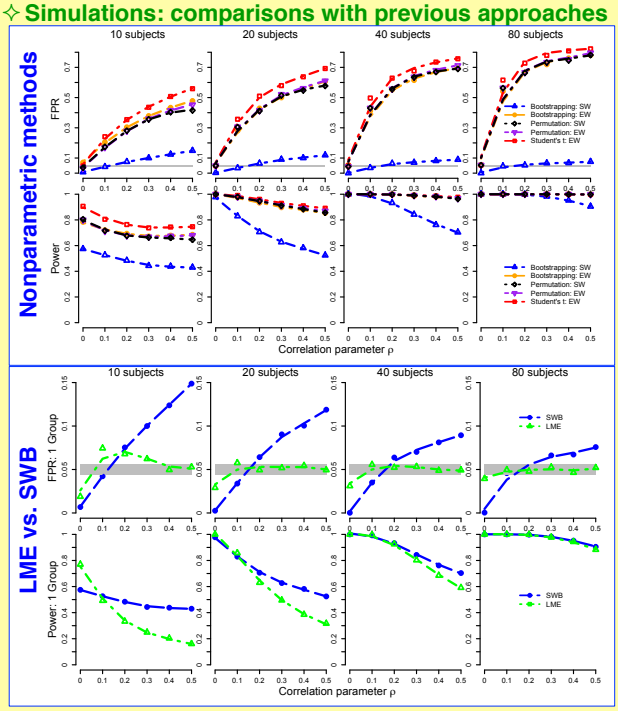
Our methods: validated via simulations & real data

✧ Methods

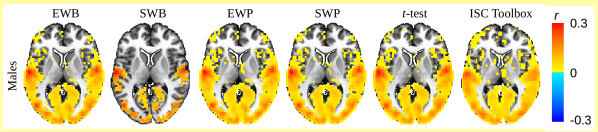
- Nonparametric: subject-wise (SW) bootstrapping/permutations [3]
- Linear mixed-effects (LME) modeling [4]

✧ Simulations: comparisons with previous approaches

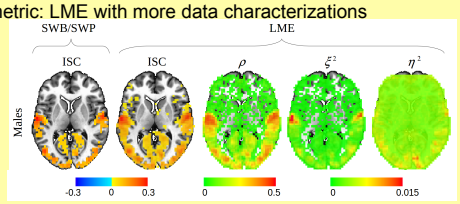


✧ Real data: comparisons with previous approaches

- 24 males; 6 movie clips; 406 time points
- Nonparametric: subject-wise bootstrapping (SWB) with best FPR control



- Parametric: LME with more data characterizations



Conclusions

- Previous methods: problematic in controlling for FPR
- Subject-wise permutations (**SWP**): ideal for comparing 2 groups
- Subject-wise bootstrapping (**SWB**): best nonparametric method for 1 group
- **LME**: valid, most flexible for all scenarios with better data characterizations

References

[1] Hasson et al., 2004. Science 303:1634-1640.
[2] Kauppi et al., 2014. Front. Neuroinform. 8:2.
[3] Chen et al., 2016. NeuroImage. doi:10.1016/j.neuroimage.2016.05.023
[4] Chen et al., 2016. Under review.