Reliability of Functional Connectivity Networks: How Can We Assess It?

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Joint work with
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A number of recent reports have examined how resting-state functional connectivity (RSFC) differs between (age or diagnostic) groups by looking at matrices of group-average correlations among \( \sim 10–110 \) regions of interest.

(Fair et al., 2008)
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We are interested in assessing the test-retest reliability of complex outcomes, in particular

1. entire correlation matrices

2. partitions into clusters (connectivity networks)

Road map: We’ll use application 1 to develop our approach, then discuss application 2.
RSFC test-retest data

- Subject scanned with fMRI for 6 minutes; told to simply relax during this period.
- Acquire BOLD time series (of length 197) at each voxel.
- Calculate average time series within each of 112 regions of interest (anatomical parcellation units; 56 in each hemisphere).
- Result: a $112 \times 112$ correlation matrix.

We obtained such matrices from 3 separate scans for each of 25 adults.

**Application 1:** What’s the “reliability” of these correlation matrices?
Regions of interest: Parcellation units

(Kennedy et al., 1998)
Correlation between a specific pair of regions

Let $z_{ij}$ be the Fisher $z$-transformed correlation between the precuneus and the amygdala for subject $i$ at session $j$ ($i = 1, \ldots, n$, $j = 1, \ldots, k$). The standard model for (univariate normal) test-retest data is a one-way random-effects ANOVA:

$$z_{ij} = \mu + \tau_i + \varepsilon_{ij}, \quad \tau_i \sim N(0, \sigma_{\tau}^2), \quad \varepsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2),$$

$$i = 1, \ldots, n, \quad j = 1, \ldots, k,$$

ICC is defined as $\text{Cor}(z_{ij}, z_{il})$ where $j \neq l$. Thus

- “population ICC” $= \frac{\sigma_{\tau}^2}{\sigma_{\tau}^2 + \sigma_{\varepsilon}^2}$;
- “sample ICC” (Shrout and Fleiss, 1979) is

$$\frac{\hat{\sigma}_\tau^2}{\hat{\sigma}_\tau^2 + \hat{\sigma}_\varepsilon^2} = \frac{MS_{btwn} - MS_{within}}{MS_{btwn} + (k - 1)MS_{within}}$$

where $MS_{btwn} = \frac{\sum_{i=1}^{n} k(\bar{z}_i - \bar{z})^2}{n-1}$, $MS_{within} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{k} (z_{ij} - \bar{z}_i)^2}{n(k-1)}$. 
Problem: Our outcomes (entire correlation matrices) are **high-dimensional** and **structured**... 

... so the ANOVA model doesn’t apply.
Another way to look at the data:
String the subdiagonal elements of each matrix into a vector to obtain an $N \times p$ matrix where

- $N = 25 \cdot 3 = 75$
- $p = 112(112 - 1)/2 = 6216(!)$

So we have a “small $N$, large $p$” problem.

Idea:

Use the distances among outcomes—rather than the outcomes themselves—to define a version of ICC.
Reliability of inter-region correlation matrices

We need:

(a) a measure of distance among correlation matrices;

(b) a distance-based definition of the ICC.
(a) Distance among correlation matrices

One possible distance (presented at Symposium in May): given two correlation matrices,

1. apply Fisher $z$ transformation to both;

2. treat the results as (6216-dimensional) vectors, and take correlation $r$ between them;

3. squared distance is then $1 - r$. 
(b) Distance-based ICC

Define between- and within-subject mean square differences

\[
B \equiv MSD_{btwn} = \frac{\sum_{i_1 > i_2} \sum_{j_1,j_2=1}^{n} (y_{i_1j_1} - y_{i_2j_2})^2}{n(n-1)k^2/2},
\]

\[
W \equiv MSD_{within} = \frac{\sum_{i=1}^{n} \sum_{j_1 > j_2} (y_{ij_1} - y_{ij_2})^2}{nk(k-1)/2},
\]

then

\[
\frac{E(B) - E(W)}{E(B)} = \frac{2(\sigma^2_T + \sigma^2_\varepsilon) - 2\sigma^2_\varepsilon}{2(\sigma^2_T + \sigma^2_\varepsilon)} = \frac{\sigma^2_T}{\sigma^2_T + \sigma^2_\varepsilon}.
\]

the population ICC. Correspondingly,

\[
\frac{B - W}{B} = \text{sample ICC}.
\]
This suggests defining a “virtual ICC”

\[ \text{vICC} = \frac{B - W}{B} \]

for arbitrary distance measures.

- Special case: the fixation index in population genetics (Excoffier, Smouse and Quattro, 1992).
75 MULTIPLE TIME SERIES

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75 INTER-REGION CORRELATION MATRICES

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vICC

75 X 75 DISTANCE MATRIX
Problems with the proposed method

• Defining distance in terms of correlation of (vectorized $z$-transformed) correlation matrices ignores differences in magnitude.

• For our 25 subjects $\times$ 3 sessions, obtained vICC=.24. (Pre-thresholding of correlations raised it to .36.)

• Can we do better?
An alternative distance for correlation matrices: Euclidean distance following dimension reduction

Recall: the vectorized $z$-transformed data matrix is $N \times p$ where

- $N = 25 \cdot 3 = 75$
- $p = 112(112 - 1)/2 = 6216$

We can reduce $p$ by

- thresholding (i.e., exclude connections for which $|r| < T$)
- taking leading principal components
- thresholding, then principal components

to obtain an $N \times p^*$ data matrix with $p^* << p$.

Then use Euclidean distance in $\mathcal{R}^{p^*}$ as the distance between correlation matrices, and thereby obtain vICC.
Results

vICC with Euclidean distance

# connections
# components

0.0 0.2 0.4 0.6
Euclidean distance vICC: Conclusions

- The best vICC values (up to .73) are obtained by taking just the first principal component score, with little or no thresholding.

- Since this is univariate, vICC reduces to regular ICC.

- Similarly, the multivariate generalization of ICC of Fleiss (1966)—Pillai trace divided by dimension (“FlICC”)—is highest (.80) with just 1 PC.

- But the first PC explains < 3% of the variance!

- Choosing number of components to maximize vICC seems wrong.
Application 2: Partitions into clusters (“networks”)

(Fair et al., 2007)
vICC for cluster partitions

• So far we’ve discussed vICC for inter-region correlation matrices.

• Next we want to define vICC for partitions of the set of regions into networks—so we need a measure of distance between cluster partitions.

• The variation of information (VI; Meilä, 2007) provides such a distance. (It’s a metric.)

• Application: Using VI as the distance, we applied \textit{K-medoids clustering} and \textit{average-linkage hierarchical clustering} to the test-retest data, for fixed values of $K$ from 2 to 15.

• Then obtained vICC for each method and each $K$. 
The VI metric: examples

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VI = 0  

VI = 0.38  

VI = 1.41
Definition of VI

Given a partition $\mathcal{C}$ of a set of points into $K$ clusters, one can define an associated probability measure $P_\mathcal{C}$ on $\{1, \ldots, K\}$, where $P_\mathcal{C}(k)$ is simply the proportion of points assigned to cluster $k$. Having defined such a probability measure for each cluster partition, one can define the information-theoretic concepts of the entropy $H(\mathcal{C})$ and the mutual information $I(\mathcal{C}, \mathcal{C}')$ between cluster partitions $\mathcal{C}, \mathcal{C}'$. The VI is then defined as $VI(\mathcal{C}, \mathcal{C}') = H(\mathcal{C}) + H(\mathcal{C}') - 2I(\mathcal{C}, \mathcal{C}')$. 
Results

![Graph showing the relationship between number of clusters and vICC for K-medoids and Average-linkage hierarchical clustering. The graph includes data points for 5, 10, 15, and 20 clusters, with vICC values ranging from 0.00 to 0.25.](image-url)
References


Thank you!