Toward Reliable Characterization of Functional Homogeneity in the Functional Connectome
Preprocessing, scan duration, imaging resolution and computational space

Xi-Nian Zuo
zuoxn@psych.ac.cn
Institute of Psychology
Chinese Academy of Sciences

BMU Networks Meeting and the Cambridge Connectome Consortium
1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d verus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
The human brain connectome is a comprehensive map of neural connections whose purpose is to illuminate brain function (Sporns, et al., 2005; Hagman et al., 2008; Bullmore and Sporns, 2009, 2012; Sporns, 2012). The functional connectome is the functional output of the brain connectome and is conceived as encompassing of brain functional networks (Biswal et al., 2010; Kelly et al., 2012; Zuo et al., 2012).
While most studies focused on brain connectivity between different units of the functional connectome, the locally functional homogeneity of a small region - regional homogeneity (ReHo) - had rarely been examined directly.
Outline

1. **Functional Homogeneity in the Human Brain**
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
     - Regional functional homogeneity (ReHo): Applications
     - Factors affect ReHo: Can we measure ReHo reliably?

2. **Imaging Data/Methodology**
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. **Main Results/Contribution**
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Measures of Functional Homogeneity

- Cross-correlation coefficients of spontaneous low frequency (COSLOF; Li et al., 2002);
- Kendall’s coefficient of concordance (KCC; Zang et al., 2004);
- Integrated local correlation (ILC; Deshpande et al., 2009);
- Local functional connectivity density (IFCD; Tomasi and Volkow, 2010).

Advantages of KCC:
1) It is a rank-based non-parametric data-driven approach, and thus allows for examining the temporally auto-correlated samples with non-normal distributions, and is more robust against noise in the data;
2) It is largely free of parametric settings and requires no a priori knowledge regarding the structure or function of the brain;
3) The computation of KCC-ReHo is relatively easy and has been implemented in software platforms with graphical user interfaces (e.g., REST, Song et al., 2011).
Outline

1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d verus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Phenotypic correlates: age, sex, intelligence and personality;

Inter-individual variability in behavioral task performance was related to the inter-individual variability of ReHo;

Clinical population: attention deficit hyperactivity disorder, schizophrenia, depression, autism spectrum disorders, obsessive-compulsive disorders, mild cognitive impairment and Alzheimer’s disease, epilepsy, Parkinson’s disease.

The detection of within- and between-group differences in ReHo suggests that KCC-ReHo may reflect stable trait properties. However, there are several factors that could impact the measure and question its reliability!
Outline

1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Factors affect ReHo

- The **physiological and neural factors** impacting other R-fMRI measures may also affect ReHo (Zuo et al., 2010);
- Some **preprocessing methods** (e.g., spatial smoothing or temporal filtering R-fMRI time series) may significantly change the ReHo magnitudes (Tian et al., 2012; Yan and Zang, 2010).

These factors raise concerns regarding the test-retest reliability of the measure and warrant its investigation!
Our aim: Comprehensively investigate the reliability

- Computing voxel-wise KCC-ReHo maps for a total 75 scans from 25 participants and estimating its intra- and inter-session TRT reliability;
- Building voxel-wise KCC-ReHo maps based on data with/without two specific preprocessing steps (i.e., smoothing and nuisance correction) to examine their influence on KCC-ReHo’s intensity and TRT reliability;
- Implementing KCC-ReHo on the cortical surface to evaluate the advantage of surface-based R-fMRI processing for ReHo;
- Computing KCC-ReHo maps using 10 min TRT R-fMRI data acquired by multi-band imaging sequences and systematically investigating the impact of temporal and spatial resolutions as well as scan durations on ReHo and their TRT reliability.
1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Two R-fMRI datasets for TRT evaluation

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age</th>
<th>TRT</th>
<th>Sequence</th>
<th>TR (s)</th>
<th>Voxel Size</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYU</td>
<td>9M, 16F</td>
<td>30.7 ± 8.8</td>
<td>45 mins 11 mons</td>
<td>EPI</td>
<td>2.0</td>
<td>3 mm</td>
<td>6.5 mins</td>
</tr>
<tr>
<td>eNKI</td>
<td>16M, 6F</td>
<td>34.4 ± 12.5</td>
<td>1 week</td>
<td>mEPI*</td>
<td>0.645</td>
<td>3 mm</td>
<td>10 mins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mEPI*</td>
<td>1.4</td>
<td>2 mm</td>
<td>10 mins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EPI</td>
<td>2.5</td>
<td>3 mm</td>
<td>5 mins</td>
</tr>
</tbody>
</table>

*Notes: mEPI = multiband EPI.

- **NYU TRT data:** [http://www.nitrc.org/projects/nyu_trt](http://www.nitrc.org/projects/nyu_trt);
- **Enhanced NKI TRT data:** [http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/FrontPage.html](http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/FrontPage.html).
Outline

1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
ReHo as both spatial and temporal filtering operations

\[ W = \frac{\sum_{i=1}^{n} (R_i)^2 - n(\bar{R})^2}{\frac{1}{12} K^2(n^3 - n)} = 12 \frac{\sum_{i=1}^{n} (\bar{R}_i)^2}{(n^3 - n)} - 3 \frac{(n + 1)}{(n - 1)}, \quad (1) \]

\( R_i (i = 1, \cdots, n) \) was denoted as the ranks of its R-fMRI BOLD timeseries and \( n \) as the number of time points. \( K \) is the number of neighbors (including the voxel, e.g., total 27 voxels used in this study) of the voxel, \( \bar{R}_i \) is the mean rank across its neighbors at the \( i \)-th time point, and \( \bar{R} \) is the overall mean ranks across all neighboring voxels and time points. The operation of computing the mean rank is equivalent to a spatial mean filtering on the rank maps.
3dReHo

KCC in Eq (1)
Functional Homogeneity in the Human Brain

- Why we care about functional homogeneity?
- Previous work on functional homogeneity
- Regional functional homogeneity (ReHo): Applications
- Factors affect ReHo: Can we measure ReHo reliably?

Imaging Data/Methodology

- Test-retest (TRT) imaging data
- ReHo algorithms: 2d versus 3d
- TRT reliability: Linear mixed models

Main Results/Contribution

- Influence of preprocessing factors
- 2dReHo: Spatial patterns and TRT reliability
- Influence of imaging resolution
- Influence of scan duration
TRT reliability: Question we ask?

\[ \text{ICC} = \frac{\text{MSb} - \text{MSw}}{\text{MSb} + (k - 1)\text{MSw}} \]

- measure
- time 1
- ?
- measure
- time 2

- slight
- fair
- moderate
- substantial
- excellent
Linear mixed models (LMMs)

\[ Y_{ij} = \lambda_0 + \text{motion}_{ij} + e_{ij}, \quad \lambda_0 = \mu_0 + p_0 + \text{age}_j + \text{sex}_j, \quad \rho = \frac{\sigma_p^2}{\sigma_p^2 + \sigma_e^2}. \] (2)

\( Y_{ij} \) denotes the \( i \)-th measurement of the \( j \)-th subject (\( i = 1, \ldots, d \) and \( j = 1, \ldots, n \)). Here, the KCC-ReHo from the \( j \)-th participant’s \( i \)-th measurement occasions. We applied a two-level LMM to each voxel as the following decomposition of \( Y_{ij} \), \( \mu_0 \) is a fixed parameter and \( p_0 \) and \( e_{ij} \) are independent random effects normally distributed with mean 0 and variances \( \sigma_p^2 \) and \( \sigma_e^2 \). The term \( p_0 \) is the participant effect and \( e_{ij} \) is the measurement error.
Outline

1 Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2 Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d verus 3d
   - TRT reliability: Linear mixed models

3 Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Nuisance correction, spatial smoothing and ILC

 Xi-Nian Zuo (IP, CAS)
1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Length-one and length-two neighboring 2dReHo

A  2dReHo (7 neighbors)
-18  -sign(T)log10(p)  18

B  Intra-session (45mins)
0.4  ICC  1.0

C  Inter-session (6mons)
0.4  ICC  1.0

D  2dReHo (20 neighbors)
-18  -sign(T)log10(p)  18

E  Intra-session (45mins)
0.4  ICC  1.0

F  Inter-session (6mons)
0.4  ICC  1.0

Xi-Nian Zuo (IP, CAS)
Outline

1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Muti-band imaging improves TRT reliability
Outline

1. Functional Homogeneity in the Human Brain
   - Why we care about functional homogeneity?
   - Previous work on functional homogeneity
   - Regional functional homogeneity (ReHo): Applications
   - Factors affect ReHo: Can we measure ReHo reliably?

2. Imaging Data/Methodology
   - Test-retest (TRT) imaging data
   - ReHo algorithms: 2d versus 3d
   - TRT reliability: Linear mixed models

3. Main Results/Contribution
   - Influence of preprocessing factors
   - 2dReHo: Spatial patterns and TRT reliability
   - Influence of imaging resolution
   - Influence of scan duration
Five minutes scan achieves good TRT reliability
Summary

- Motion and non-brain tissue correction significantly improve the ReHo’s reliability;
- Global brain signal regression significantly reduces the ReHo’s reliability;
- 5 min scan duration is enough to achieve reliable ReHo estimates;
- Surface-based analysis produces highly reliable ReHo measures;
- Multi-band EPI resting-state brain dramatically increases the reliability.

Limitation and Direction

- **Head motion** has complex relationships with age and various R-fMRI metrics at the group level;
- Numerous **physiologic processes** (e.g., cardiac and respiratory) can contribute artifactual signals to R-fMRI data;
- Develop **mean filtering strategy for 2dReHo** by using diffusion filters on the manifold of the cortical surface.
Lab Members
Collaborators

Michael Peter Milham, Child Mind Institute at New York City;
F. Xavier Castellanos, Institute for Pediatric Neuroscience at New York University;
Yu-Feng Zang, Center for Cognition and Brain Disorders, Hangzhou Normal University;
Yong He, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University;
Olaf Sporns, Indiana University.
Grants

- National Natural Science Foundation of China (81220108014, 81171409, 81030028);
- Open Research Fund of the Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences;
- Startup Foundation for Distinguished Research Professor (Y0CX492S03), Institute of Psychology, Chinese Academy of Sciences;
- NIMH (R01MH083246), USA.
For Further Reading I

O. Sporns.  
*Discovering the Human Connectome.*  

E. Bullmore and O. Sporns.  
Complex brain networks: graph theoretical analysis of structural and functional systems.  

E. Bullmore and O. Sporns.  
The economy of brain network organization.  

X.N. Zuo, et al.  
Toward reliable characterization of functional homogeneity in the human brain: Preprocessing, scan duration, imaging resolution and computational space.  
For Further Reading II

X.N. Zuo, et al.

B.B. Biswal, et al.

C. Kelly, et al.

Y.F. Zang, et al.