Uncovering Multi-Site Identifiability Based on Resting-State Functional Connectomes

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Abstract

Multi-site studies are becoming important to increase statistical power, enhance generalizability, and to improve the likelihood of pooling relevant subgroups together—activities which are otherwise limited by the availability of patients or funds at a single site. Even with harmonized imaging sequences, site-dependent variability can mask the advantages of these multi-site studies. The aim of this study was to assess multi-site reproducibility in resting-state functional connectivity “fingerprints”, and to improve identifiability of obtained functional connectomes. The individual fingerprinting of functional connectivity profiles is promising due to its potential as a robust neuroimaging biomarker with which to draw single-subject inferences. We evaluated individual fingerprints in test-retest visit pairs within and across two sites and present a generalized framework based on principal component analysis to improve identifiability. Those principal components that maximized differential identifiability of a training dataset were used as an orthogonal connectivity basis to reconstruct the individual functional connectomes of training and validation sets. The optimally reconstructed functional connectomes showed a substantial improvement in individual fingerprinting of the subjects within and across the two sites and test-retest visit pairs relative to the original data. A notable increase in ICC values for functional edges and resting-state networks were also observed for reconstructed functional connectomes. Improvements in identifiability were not found to be affected by the presence or absence of global signal regression. Result demonstrate that the data-driven method presented in this study can improve identifiability in resting-state functional connectomes in multi-site studies.

1 Introduction

Multi-site functional magnetic resonance imaging (fMRI) studies are increasingly important for understanding the structure and function of a healthy brain and also subsequent to neuropathology. Recent examples of multi-site imaging initiatives include
The Human Connectome Project [1, 2], the 1,000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org), and disease-oriented initiatives such as the Functional Biomedical Informatics Research Network for schizophrenia [3] and the Alzheimer’s Disease Neuroimaging Initiative [4], among others [5]. Multi-site studies achieve larger sample sizes by including cohorts recruited at the different sites. On one hand this allows for higher statistical power and better generalization of the results than may be achieved with potentially limited availability of patients or funds at a single site. On the other hand proper assessment of these data requires principled methodologies, including multivariate analyses coupled with cross-validation designs [4, 5, 6, 7, 8]. Known challenges in multi-site acquisitions and their subsequent analyses include the scanner-dependent variability that can mask true underlying changes in brain structure and function. Even when using identical (let alone “comparable”) imaging sequences and parameters, potential site-dependent differences might arise due to a range of physical variables, including field inhomogeneities, transmit and receive coil configurations, system stability, system maintenance, scanner drift over time and many others [5, 6, 9]. Determining and minimizing these unwanted site-dependent variations have become critical elements in the design of multi-site fMRI studies.

Many studies have investigated the variation and stability of simple behavioral, motor or memory tasks in multiple sites using fMRI. Such studies have typically used ANOVA models or variance component analysis to examine the variability and extent of overlap of activation maps in task-based fMRI scans acquired across multiple sites [8, 9, 10, 11, 12, 13, 14, 15].

In contrast, only a few studies have assessed the variations in resting-state fMRI across sites. These studies used variance component analysis, intra class correlation (ICC) coefficient and/or coefficient of variance to evaluate inter-site and inter-subject variability in connectivity scores, cluster size and temporal signal-to-noise ratio in regions of interest for default mode networks derived from seed-based or independent component analysis [16, 17, 18, 19, 20, 21].

Resting-state fMRI (rs-fMRI) measures the spontaneous neural activity in the brain and determines the default functional connectivity between brain regions. rs-fMRI has gained widespread attention and is used to investigate brain functional connectivity in the normal healthy brain [22, 23, 24, 25] as well as in many clinical populations [26, 27, 28]. In recent years, a family of methods has become popular that applies graph theory methods to investigate functional connectivity [29, 30, 31, 32, 33]. In this context, the correlations between blood oxygenation level dependent (BOLD) signals observed in different brain regions determine the edges of the graphs, with these edges referred to as a functional connectome (FC). Various graph theoretical measures may be used to investigate the organization of underlying relevant networks [33].

One important avenue of investigation is to explore differences in FC profiles at an individual, rather than group, level [34]. Group averages represent robust connectivity patterns, but inherently mask subject-specific features. Differences in FC profiles in individuals, relative to the group level, have been demonstrated [35, 36, 37, 38, 39, 40, 41, 42, 43, 44] and may help in developing robust neuroimaging-based biomarkers, or even for making subject-level inferences. Robust individual differences in functional connectivity have been termed “fingerprints”, and may be demonstrated by the self-identification of subjects by correlating test and retest visits over a body of subjects [36, 44, 45, 46, 47, 48]. Fingerprinting relies on the fact that subjects are expected to exhibit an inter-session variability that is less than the inter-subject variability (i.e., they resemble themselves across visits more strongly than they resemble other subjects). The ability to pair the FCs coming from the same subject reflects the inherently high identifiability of the connectivity dataset.

This study explores the unanswered question of variability in the identifiability of
subjects in a multi-site scenario, providing a framework to minimize the unwanted site-dependent variations and enhance identifiability on functional connectomes. To date, identifiability has been studied where test and retest rs-fMRI scans have been conducted in the strictly controlled scenario involving the same scanner, the same imaging sequences, same-day image acquisitions, and constant processing over all data [36, 44, 47]. For example, Amico et al., [44] determined the identifiability of subjects based on a single test-retest visit on one site. Herein we extend the investigation of identifiability by relaxing a number of these conditions. In particular, we use two different scanners, allow the number of days between repeated visits to vary, and assess the impact of global signal regression as part of the data processing pipeline. We optimally reconstructed the FCs using those principal components that maximized average identifiability across all visits, thereby and serving as an orthogonal basis for the connectivity. This was performed both with and without global signal regression. For each of these cases, we then compared the identifiability obtained from the original and optimal reconstructed FCs. In all cases, the reconstruction process produced significantly enhanced identifiability across imaging systems, providing strong motivation for application of this approach to increase the statistical power and generalizability of results for multi-site fMRI studies.

2 Methods

2.1 Participants

A cohort consisting of 23 undergraduate and graduate students (12 male and 11 female; ages 18-28) participated in a total of four imaging sessions (0-21 days apart) at two sites. None of the participants reported any history of neurological disorders. At site1 two imaging sessions were conducted using a 3T General Electric Signa HDx and a 16-channel brain array (Nova Medical). At site2 two imaging sessions were conducted using a 3T GE Discovery MR750 and a 32-channel brain array (Nova Medical). The two imaging sessions at a given site were conducted on the same day (i.e., 0 days apart).

2.2 MRI Data Acquisition

Each imaging session (independent of site) consisted of a structural T1 weighted scan and two rs-fMRI scans (test and retest, eyes open and 9 min and 48 sec). The high-resolution T1 scan used for registration and segmentation purposes consisted of 3D fast spoiled gradient recalled echo sequence: TR/TE = 5.7/1.976 msec; flip angle = 73°; 1 mm isotropic resolution and the rs-fMRI scans with common imaging parameters across sites consisted of blipped echo-planar imaging: TR/TE = 2,000/26 msec; flip angle = 35°; 34 slices; acceleration factor = 2; Field of View = 20 cm; 3.125 x 3.125 x 3.80 mm voxel size and 294 volumes.

Note that eight rs-fMRI scans were conducted in total on each subject (see Figure 1) and divided into a training dataset and a validation dataset. The two runs acquired in the first session at each of the two sites (four total) were incorporated into the training set. Similarly the remaining four rs-fMRI scans, those corresponding to the two runs acquired in the second imaging session at each site, were incorporated into the validation set.

2.3 Data Processing

rs-fMRI data were processed using functions from AFNI [49] and FSL [50, 51] using in-house MATLAB code following steps from [52]. Structural T1 images were first denoised using the filters described in [53, 54, 55] (using FSL fsl_anat) to improve signal-to-noise...
ratio and effect bias-correction. Images also underwent intensity normalization (AFNI 3dUnifize). Structural images were then segmented (FSL FAST) into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) tissue masks.

rs-fMRI BOLD timeseries were processed in the subject’s native space. The first four volumes were discarded to remove spin history effects, leaving 290 volumes for processing. The 4D BOLD timeseries was then passed through outlier detection (AFNI 3dToutcount), despiking (AFNI 3dDespike), slice timing correction (AFNI 3dTshift), and subsequently underwent volume registration (AFNI 3dvolreg) to the minimized bounding volume. The rs-fMRI BOLD timeseries were then aligned to the T1 structural scan (AFNI align_epi_anat.py). Voxel-wise spatial smoothing was applied independently within each of the GM, WM and CSF masks, using a 4mm full-width-at-half-maximum isotropic Gaussian Kernel (AFNI 3dBlurinMask). The resulting BOLD timeseries were then scaled to a maximum (absolute value) of 200, and data were censored to remove outlier timepoints. Censoring of individual rs-fMRI volumes occurred if the motion derivatives had a Euclidean norm [56] above 0.4. Censoring involved removal not only of the volume at which this high norm was observed, but also the immediately preceding and following volumes, given that effects of motion are carried across timepoints. Entire rs-fMRI timeseries were discarded if more than 100 volumes (34% of the volumes) were censored. Only the subjects for which all eight rs-fMRI scans survived motion censoring were included in the analysis.

The above procedure resulted in a net dataset of 128 rs-fMRI scans, representing eight runs from each of 16 participants. These runs were evaluated after being detrended by one of two approaches, one with global signal regression (GSR), and one without (NoGSR). Both detrending (AFNI 3dDeconvolve) approaches incorporated the following common regressors: (1) very low frequency fluctuations as derived from a bandpass [0.002-0.01Hz] filter (AFNI 1dBport); (2) the 12 motion parameters, consisting of three linear translations [x,y,z], three rotations [pitch, yaw, roll] and the corresponding set of first derivatives [57, 58]; and (3) the voxel-wise local neighborhood (40mm) mean WM timeseries (AFNI 3dTproject) [59]. The data at this point represent the NoGSR dataset. Incorporation of a fourth regressor source—the whole-brain mean GM timeseries—in the detrending stage results in the GSR dataset.

For connectivity analysis on a regional basis, the atlas from [60] was warped to each subject’s native space by linear and non-linear registration (AFNI auto_warp.py and 3dAllineate). This permitted GM to be partitioned into 278 regions of interest (ROIs). Note that data from the cerebellum (30 ROIs) were discarded, because the acquired volume did not completely cover this structure for all subjects. This resulted in a final GM partition of 248 ROIs.

A functional connectivity matrix (namely the functional connectome; FC) was computed for each rs-fMRI scan through cross-correlation of the mean time series from each of the 248 ROIs (MATLAB command corr). The resulting square, symmetric FC matrices were not thresholded or binarized. Each FC matrix was ordered into seven cortical sub-networks, as proposed by Yeo et al. [61], and an additional eighth sub-network comprising sub-cortical regions was added [52]. This resulted in eight functional connectomes per subject (four from each site; two training and two validation).

2.4 Differential Identifiability extended for Multi-Site

The upper triangular portion of each FC (test and retest) for the training data was vectorized and added to a matrix where the columns were runs and the rows represent the functional connectivity patterns. Hence, this matrix had \( \binom{248}{2} \) rows and 64 columns (four runs per subject; 16 subjects). Principal component analysis (PCA) was used to extract M = 64 principal components (i.e., functional connectivity eigenmodes) from the vectorized training dataset (MATLAB command pca). The principal components
(PCs) were arranged in descending order of their explained variance. These PCs were then projected back into each subject’s FC space to obtain individual reconstructed functional connectomes as analogously done by Amico et al. [44]. Below we extend this approach for multi-site acquisitions.

For individual fingerprints of subjects within and across sites, the identifiability matrix ($I$) was created by correlating the subjects’ test and retest FCs within and across the two sites. This gave rise to a multi-site identifiability matrix, $I$ which consisted of Pearson’s correlation coefficients. For the particular case of two imaging sites, the test-retest combinations created four blocks ($I^{ij}$) in the identifiability matrix $I$,

$$I = \begin{bmatrix} I^{11} & I^{12} \\ I^{21} & I^{22} \end{bmatrix}$$

where $I^{ij}$ contained Pearson’s correlation coefficient obtained by correlating FCs from the site $i$ test session with the FCs from the site $j$ retest session. $I^{11}$ and $I^{22}$ represent the fingerprinting of the subjects within the two sites and $I^{12}$ and $I^{21}$ represent the fingerprinting of the subjects across the two sites.

For each test-retest [site $i$, site $j$] pair, differential identifiability ($< I^{ij}_{diff} >$) was calculated from the block $I^{ij}$ following the procedure from [44]

$$< I^{ij}_{diff} > = < I^{ij}_{self} > - < I^{ij}_{others} >$$

where

$$< I^{ij}_{self} > = \frac{1}{N} \sum_{k=1}^{N} I^{ij}_{self}(k)$$

$$I^{ij}_{self}(k) = I^{ij}_{kk}, \quad \forall \, k = 1, 2, \ldots, N$$

Here $N=16$ is the number of subjects.

$I^{ij}_{self}$, defined as self identifiability, is a vector of length $N$ and contains the main diagonal elements $I^{ij}_{self}(k)$ of the block $I^{ij}$, and denotes the correlation between the repeat visits of the same subject. The average of the main diagonal elements for the block $I^{ij}$, $< I^{ij}_{self} >$, represents the overall self correlation for the [site $i$, site $j$] pair.

$$< I^{ij}_{others} > = \frac{1}{N} \sum_{k=1}^{N} I^{ij}_{others}(k)$$

$$I^{ij}_{others}(k) = \frac{1}{2} \left( \frac{1}{N-1} \sum_{l=1}^{N} I^{ij}_{kl} + \frac{1}{N-1} \sum_{l=1}^{N} I^{ij}_{lk} \right), \quad \forall \, l \neq k$$

For the $k$-th subject $I^{ij}_{others}(k)$ is an element of the vector $I^{ij}_{others}$ and is obtained by the average of the $k$-th row and $k$-th column, excluding the main diagonal entry of the block $I^{ij}$, and defines the average correlation of the $k$-th subject’s FCs (test and retest) with all other subjects. $< I^{ij}_{others} >$ is the average of all $I^{ij}_{others}(k)$ of the block $I^{ij}$, and defines an overall mean correlation between visits of different subjects for the [site $i$, site $j$] pair.

For visits associated with the [site $i$, site $j$] pair, $< I^{ij}_{diff} >$ characterizes the difference between the average within-subject FC similarity and the average between-subject FC
similarity. The higher the value of $< I_{diff}^{ij} >$, the stronger is the overall fingerprinting of the population for the [sitei, sitej] pair.

To maximize the fingerprinting of the population across all the [sitei, sitej] visit pairs, the average of the four $< I_{diff}^{ij} >$ values was used, where

$$< < I_{diff} >> = \frac{1}{4} \sum_{i=1}^{2} \sum_{j=1}^{2} < I_{diff}^{ij} >$$

$< < I_{diff} >>$ is then maximized by the selection of subsets of $m$ PCs from the total number (here $M = 64$) of PCs obtained from the training set. For each subset of the first $m$ PCs, the subjects’ test-retest FCs were reconstructed, and $< < I_{diff} >>$ was calculated from these data. The optimal number of PCs, $m^*$, maximizes the value of $< < I_{diff} >>$, namely $< < I_{diff}^* >>$, as given by [44]:

$$< < I_{diff}^* >> = \arg\max_{m \in M} < < I_{diff} >> (m)$$

The $m^*$ PCs were used to reconstruct the individual FCs (for both visits—i.e., test and retest) for the training and validation sets. The identifiability matrices computed from the original and reconstructed data for each of the training and validation sets were then compared.

Analogously, when focused on a particular [sitei, sitej] visit pair, we may obtain $m_{ij}^*$ as

$$< I_{diff}^{ij}^* > = \arg\max_{m_{ij} \in M} < I_{diff}^{ij} > (m)$$

### 2.5 Statistical Analysis

Differential Identifiability ($I_{diff}^{ij}$) was computed for each [sitei, sitej] pair from $I^{ij}$ as follows

$$I_{diff}^{ij} = I_{self}^{ij} - I_{others}^{ij}$$

For the $k$-th subject the value of $I_{diff}^{ij}(k)$ was calculated as

$$I_{diff}^{ij}(k) = I_{self}^{ij}(k) - I_{others}^{ij}(k)$$

$I_{diff}^{ij}(k)$ characterizes the differential identifiability on a subject level and quantifies the difference between the $k$-th subject’s FC self identifiability and its similarity with other subjects’ functional connectomes. The higher the value of $I_{diff}^{ij}(k)$, the higher is the identifiability of the $k$-th subject among the cohort.

Pairwise comparisons were done on the distributions of $I_{diff}^{ij}$ obtained from the original and reconstructed data, for both the training and validation sets, using the Wilcoxon signed rank test followed by a Bonferroni correction on each subset of tests (e.g., four tests were conducted on the each of the NoGSR and GSR training and validation sets, so a correction for four tests was performed). All such analyses were conducted in R [62]. Any pairwise comparison was considered significant if $p_{Bonferroni} < 0.05$. Similar comparisons were also made between the distributions of $I_{diff}^{ij}$ as obtained from reconstructions for original data with (GSR) and without (NoGSR) global signal regression.

The intraclass correlation coefficient (ICC) was used to assess the agreement of an edge (functional connectivity value between two brain regions) between visits of subjects on each [sitei, sitej] pair. ICC [63, 64] is generally used to assess the agreement between measurements for different groups. The stronger the resemblance between the measurements, the higher is the ICC value. A bootstrap procedure was applied to compute ICC to avoid values that are biased by a small subset of the population. In
Figure 1: Resting-state fMRI acquisitions: Subjects (N=23) underwent two imaging sessions (Training and Validation) at each of two MRI sites (Site1 and Site2), wherein each session comprised two resting-state runs (test and retest). This setup produced a total of eight runs and associated functional connectome (FC) measures per subject.

Each of 100 iterations 75% of the population was selected at random, and the ICC was calculated for each edge. The averages over all iterations were used to compare the edgewise ICC values of the original and the reconstructed data. ICC values for the resting-state functional networks of [65], for both the original and reconstructed data, were computed by averaging over the ICC values for the edges that belonged to each functional network.

Using the aforementioned Bootstrap procedure, the edgewise ICC was also computed from all four visits across the two sites and these edgewise ICC were averaged over each brain region from [60] to compare the reproducibility, between training and validation sets, of connectivity in each brain region across the original and reconstructed data.

The procedure above was repeated for each of the GSR and NoGSR datasets.

3 Results

The dataset used for this study consisted of two fMRI sessions (each session consisted of test and retest pair of rs-fMRI scans) per subject on two different sites. After quality checks, 16 subjects with eight FCs per subject were used (see Methods). Building upon [44], we here expanded the concept of identifiability for multiple acquisitions on multiple sites. We evaluated this method by splitting our dataset (see Figure 1) into training and validation sets. The training dataset consisted of four FCs per subject (test-retest at sitel, test-retest at site2). Analogously, the validation dataset consisted of another four FCs per subject (for the same subjects as the training dataset; test-retest at sitel, test-retest at site2).

When assessing the training dataset, FCs were decomposed and subsequently recon-
constructed based on PCA by using each subset of first $m$ number of components out of the total ($M = 64$). For each number of PCA components $m$, $\langle I_{diff} \rangle$ was computed from the reconstructed data (see Methods) and compared to $\langle I_{diff} \rangle$ obtained from original data. Figure 2 shows $\langle I_{diff} \rangle$ computed from the original and, iteratively, from the reconstructed data as a function of $(m)$, the number of PCs preserved. $\langle I_{diff} \rangle$ peaked at $m^* = 18$ for both NoGSR and GSR datasets. These $m^*$ PCs extracted from the training set were used as a fixed orthogonal connectivity basis (i.e. PCA loadings) to reconstruct the functional connectomes (denoted by Recon) of the training and validation sets for comparing identifiability obtained from the original FCs (Orig).

When looking at $\langle I_{ij}^{ij} \rangle$ for different $[site_i, site_j]$ visit pairs for NoGSR and GSR, we found different optimal numbers of components ($m^{ij}$). A summary of $\langle I_{ij}^{ij} \rangle$ and the corresponding $m^{ij*}$ for all configurations is shown in Table 1. Note how the identifiability profiles....

Identifiability matrices ($I$) consisting of Pearson’s correlation coefficient between FCs of subjects’ test and retest visits across and within the two sites were computed, expanding on [44]. The identifiability matrices obtained from reconstructed FCs using $m^*$ PCs were compared to the ones obtained from original data. Figure 3 illustrates that the identifiability matrices obtained from optimally reconstructed functional connectomes outperformed the original FCs. The individual fingerprint of the subjects (main diagonal of each block $I^{ij}$) within and across the sites were stronger after the optimal reconstruction for both NoGSR and GSR datasets.

Differential Identifiability ($I_{diff}^{ij}$) for each $[site_i, site_j]$ pair was computed from $I^{ij}$ blocks (see Methods). The distributions of $I_{diff}^{ij}$ obtained from original and optimally reconstructed data were compared. Figure 4 shows that the distributions of $I_{diff}^{ij}$ for each $[site_i, site_j]$ pair was significantly higher ($p_{FDR} < 0.05$, Wilcoxon signed rank test) after optimal reconstruction of the data, indicating higher identifiability of the subjects among the cohort. This result held for both the NoGSR and GSR cases.

The group averages of original and optimally reconstructed FCs using $m^*$ PCs were computed. Figure 5 shows that the group average of original and reconstructed functional connectomes were almost identical, indicating that the optimal PCA reconstruction preserved the main group-level characteristics of the functional connectomes for both NoGSR (Figure 5 A-B) and GSR (Figure 5 C-D) datasets.

ICC was used to assess the reproducibility of edges in functional connectomes between visits of subjects within and across the two sites. The average ICC value, over 100 iterations obtained from the bootstrap procedure (see Methods for details), from original and optimally reconstructed FCs were compared. ICC for each functional network was computed by averaging over ICC values for all the edges that belonged to a functional network. Figure 6,7 shows the edgewise ICC averaged over 100 iterations for the original and the reconstructed data. The edgewise ICC largely increased after optimal reconstruction for almost all edges (Tables 2, 3) for each $[site_i, site_j]$ pair for NoGSR (Figure 6,7 A-B) and GSR (Figure 6,7 C-D) datasets. Figure 8 shows that the average ICC for each functional network in the reconstructed data was also higher than in the original data.

When integrating test-retest FC data from both imaging sites, we measured edgewise ICC, pooling all four visits per subject. Figure 9 shows the edgewise ICC and histograms for average ICC for each brain region (using the atlas from [60]) for the original and reconstructed data in the validation set. Figure 10 presents a brain rendering overlaid with the averaged edgewise ICC values of each brain region as computed from all four test-retest visits across the two sites using the validation dataset. The edgewise ICC and value per brain region for optimally reconstructed data indicated higher reproducibility of the functional connectomes. Both edgewise and average brain region ICC
Figure 2: Average percentage differential identifiability ($\ll \hat{I}_{diff} \gg \times 100$) and differential identifiability of each [site $i$, site $j$] pair, ($\ll \hat{I}^{ij}_{diff} \gg \times 100$) for training data as a function of the number of principal components (PCs) used for reconstruction for resting-state data without global signal regression (NoGSR; (A) and (B)); and with global signal regression (GSR; (C) and (D)). In all figures solid lines denote $\ll \hat{I}_{diff} \gg$ and $\ll \hat{I}^{ij}_{diff} \gg$ as computed from the original FCs, whereas lines with circles denote the differential identifiability for reconstructed FCs as a function of $m$, the included number of components. In (A) and (C), the gray (shaded) area denotes the 95% confidence interval for $\ll \hat{I}_{diff} \gg$ over 100 random permutations of the test-retest FC pairs at each value of $m$.

increased after optimal reconstruction from $m^*$ PCs, indicating higher reproducibility and identifiability of the reconstructed functional connectomes as compared to the original ones.

4 Discussion

Recently the concepts of brain fingerprinting and identifiability have been investigated based on repeated measures of individual whole-brain estimates of resting-state functional connectivity [35, 36] and between fMRI tasks [37, 42, 47]. More recently, Amico et al. [44] introduced the concept of an identifiability matrix to assess the fingerprinting of a dataset through a functional denominated identifiability score (see Methods). Further they introduced a data-driven method to uncover identifiability in whole-brain functional connectomes (FCs) based on principal component decomposition and subsequent reconstruction. Here, we extended this framework for multi-site repeated measurements experiments and show how high identifiability on an inter-scanner basis is achievable.
Figure 3: Identifiability matrices (I) of the original (Orig) and reconstructed (Recon) data for the Training, (A) and (C), and Validation, (B) and (D) sets of resting-state functional connectomes without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). The Identifiability matrix (I) has a blockwise structure where each block is $I^{ij}$, representing the identifiability for the [site$i$, site$j$] pair.

Table 1: Maximum percentage differential identifiability ($< I^{ij}_{diff} > \times 100$) and number of principal components for each [site$i$, site$j$] pair ($m^{ij}$) for Training datasets without global signal regression (NoGSR) and with global signal regression (GSR).

| [site$i$, site$j$] | $I^{ij}_{diff}$ | $m^{ij}$ |
|-------------------|----------------|---------|
| site1, site1      | 46.7           | 29      |
| site1, site2      | 32.9           | 17      |
| site2, site1      | 32.1           | 17      |
| site2, site2      | 45.7           | 29      |

| [site$i$, site$j$] | $I^{ij}_{diff}$ | $m^{ij}$ |
|-------------------|----------------|---------|
| site1, site1      | 46.0           | 34      |
| site1, site2      | 33.4           | 18      |
| site2, site1      | 33.5           | 18      |
| site2, site2      | 45.1           | 33      |
Figure 4: Box plots of Differential Identifiability ($I_{ij}^d$) computed from each block of the Identifiability matrix (i.e., $I_{ij}$) for the original (Orig) and optimally reconstructed (Recon) data without global signal regression ($\text{NoGSR}$; (A) and (B)) and with global signal regression ($\text{GSR}$; (C) and (D)). Values of Pearson’s $r$ that are significantly higher ($p_{\text{Bonferroni}} < 0.05$, Wilcoxon signed rank) for Recon relative to Orig are marked by double asterisks. Note that no statistically significant effect of exclusion/inclusion of global signal regression was observed in distributions of $I_{ij}^d$. 


Figure 5: Evaluation of PCA reconstruction at the optimal number of components ($m^* = 18$) for resting-state functional connectomes (FCs) data without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). Left-to-right in each of (A)-(D): the group averaged FC of the original (Orig) data; the group averaged FC of the reconstructed (Recon) data; the scatter plot (for all edges) of the Recon group-averaged FC (y-axis) vs. the Orig group-averaged FC (x-axis).

Table 2: Percentage of positive and negative edgewise intra-class correlation coefficient (ICC) values (computed for each FC edge and averaged over 100 iterations; see Methods for Bootstrap procedure) of original (Orig) data that were converted to positive or negative edgewise ICC in reconstructed (Recon) data for resting-state functional connectomes without global signal regression (NoGSR).

| [site1, site1] | Training Set | Validation Set |
|----------------|--------------|----------------|
|                | Recon        | Recon          |
| Orig Negative  | 0.95         | 0.20           |
| Positive       | 0.01         | 0.00           |
| Orig Negative  | 95.05        | 99.80          |
| Positive       | 99.99        | 100.00         |

| [site1, site2] | Training Set | Validation Set |
|----------------|--------------|----------------|
|                | Recon        | Recon          |
| Orig Negative  | 14.34        | 3.92           |
| Positive       | 0.77         | 0.29           |
| Orig Negative  | 85.66        | 96.08          |
| Positive       | 99.23        | 99.71          |

| [site2, site1] | Training Set | Validation Set |
|----------------|--------------|----------------|
|                | Recon        | Recon          |
| Orig Negative  | 12.10        | 11.19          |
| Positive       | 0.53         | 1.03           |
| Orig Negative  | 87.90        | 88.81          |
| Positive       | 99.47        | 98.97          |

| [site2, site2] | Training Set | Validation Set |
|----------------|--------------|----------------|
|                | Recon        | Recon          |
| Orig Negative  | 0.00         | 0.58           |
| Positive       | 100.00       | 99.42          |
| Orig Negative  | 100.00       | 0.03           |
| Positive       | 0.03         | 99.97          |
Figure 6: Scatter plots of averaged (100 iterations) intra-class correlation coefficient (ICC) values, computed over each FC edge, for the reconstructed (Recon) data (y-axis) versus the edgewise ICC for the original (Orig) data (x-axis). Plots are presented for data without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). In each plot, quadrants are colored for clarity of the effect of reconstruction on ICC values. Blue represents positive values in both Orig and Recon; green represents negative Orig and positive Recon; black represents negative values for both Orig and Recon; and red represents positive Orig and negative Recon.
Figure 7: Averaged (100 iterations) intra-class correlation coefficient (ICC) values, computed for each FC edge, for the original (Orig) and reconstructed (Recon) on the Training and Validation sets, for resting-state functional connectomes without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). Edges are arranged by Yeo’s resting-state functional networks [65].

Table 3: Percentage of positive and negative edgewise intra-class correlation coefficient (ICC) values (computed for each FC edge and averaged over 100 iterations; see Methods for Bootstrap procedure) of original (Orig) data that were converted to positive or negative edgewise ICC in reconstructed (Recon) data for resting-state functional connectomes with global signal regression (GSR).
Figure 8: Intra-class correlation coefficient (ICC) values for each functional network, computed as the average of edgewise ICC over each of Yeo’s resting-state functional networks in the original (Orig) and reconstructed (Recon) data for Training and Validation sets on resting-state functional connectomes without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). Yeo’s resting functional networks [65]: Visual (VIS), Somato-Motor (SM), Dorsal Attention (DA), Ventral Attention (VA), Limbic system (L), Fronto-Parietal (FP), Default Mode Network (DMN), and subcortical regions (SUBC).
Figure 9: Averaged (100 iterations; see Methods for bootstrap details) intra-class correlation coefficient (ICC) values, computed for each FC edge from four visits across two sites, for the Validation set original (Orig; (A) and (B)) and reconstructed (Recon; (C) and (D)) data without global signal regression (NoGSR; (A) and (C)) and with global signal regression (GSR; (B) and (D)).

at the whole-brain level, as well as at the pairwise level for functional edges. This approach to uncover identifiability was equally effective for rs-fMRI data processed with and without global signal regression. Results indicate that the individual fingerprints obtained from optimally reconstructed FCs were robust, and improved identifiability among the cohort. Further, the method improved the reproducibility of the functional connectivity profiles across visits, both on an edgewise and functional network basis.

Average differential identifiability \( \langle I_{diff} \rangle \) was used as a quality function to maximize the fingerprinting of individual subjects within a cohort by exploring connectivity subspaces over a range of M principal components. The identifiability of a connectivity profile of a subject relies on the fact that individual subjects are expected to be most similar to themselves across visits or scanning sessions, relative to others. We used a continuous identifiability score as defined by [44] for individual fingerprinting of subjects in test-retest sessions for two sites. The continuous identifiability score, \( < I_{diff} > \), quantified the difference between average within-subject similarity and average between-subject similarity for a single [sitei, sitej] visit pair. \( < I_{diff} > \) quantified the overall fingerprinting of the population across all test-retest visits. \( < I_{diff} > \) was then maximized over subsets of M PCs to find the \( \mathbf{m}^* \) PCs that maximized differential identifiability and provided the optimal orthogonal basis to reconstruct the FCs. For both the NoGSR and GSR datasets, \( < I_{diff} > \) and \( < I_{diff}^0 > \) (Figure 2) showed a significant improvement over the identifiability score computed from the original FCs. The higher value of average differential identifiability indicates stronger overall individual fingerprinting of the population.

When assessing \( < I_{diff}^0 > \) and \( m_{ij}^* \) (see Table 1), it can be seen that there are differences in the proportion of the dimensionality of the data that are kept for maximizing identifiability. In particular, visit pairs including different sites (i.e., [site1, site2] and [site2, site1]) had \( m_{ij}^* \) values very close to the number of subjects (i.e., 16) whereas visit
Figure 10: Brain rendering of intraclass correlation coefficient (ICC), computed from all four visits across the two sites for the Validation set original (Orig; (A) and (C)) and reconstructed (Recon; (B) and (D)) data without global signal regression (NoGSR; (A) and (B)) and with global signal regression (GSR; (C) and (D)). The strength per brain region—computed as the mean of edgewise ICC values (ICC computed for each FC edge and averaged over 100 iterations; see Methods for Bootstrap procedure)—provides an assessment of overall reproducibility of the functional connections of each brain region.
pairs including just one site (i.e., [site1, site1] and [site2, site2] were able to keep a larger number of components, indeed approximately the number visits within an imaging site (i.e., twice the number of subjects). These results emphasize how important it is to formalize a data-driven framework for reconstruction of FCs that is not based on fixing certain number of components or ultimately a percentage of variance, since identifiability might peak at very different configurations depending on multiple factors, including number of subjects, number of imaging sites, baseline similarity between test-retest on the sites, etc.

Identifiability matrices (I) computed from optimally reconstructed data outperformed those computed from the original data. Identifiability matrices consisted of Pearson’s correlation coefficient between FCs corresponding to subjects’ test and retest visits, within and across the two sites. The main diagonal of each of the four blocks (I^j_{ij}) consisted of correlations between visits of the same subject within and across the two sites. These self correlations had higher values in I obtained from optimally reconstructed data as compared to the ones obtained from original data (Figure 3). One of the noteworthy facts about Figure 3 is the substantial increase in self correlations for the challenging problem of test-retest visits between the two sites. This indicates stronger individual fingerprints of subjects after optimal reconstruction of the FCs, not only in repeated visits within the same site, but also among visits across two sites.

Statistically higher values for the distributions of I^j_{diff} for all test-retest [sitei, sitej] pairs of the reconstructed data as compared to the original data illustrated stronger fingerprinting of the population. I^j_{diff} quantified the differential identifiability on a subject level for the test-retest [sitei, sitej] pairs. Higher I^j_{diff} values indicated improved identifiability of subjects. Differential identifiability increased for all subjects within the same site visits, and also between the two sites after optimal reconstruction of the FCs. No difference was found in the reconstructed data between distributions for NoGSR and GSR I^j_{diff}, suggesting that both approaches benefit from this framework, both within and between sites in a similar way.

The group averages of the original and optimally reconstructed FCs were almost identical, indicating that the main group level features of the functional connectivity profiles were preserved by the optimal reconstruction. The m* PCs that maximized the \(< < I_{diff} >>\) obtained from the training data, were used as an optimal orthogonal basis to reconstruct the functional connectivity profiles for subjects’ test and retest sessions in both the training and validation sets. In general PCA is used to transform a set of correlated variables into a set of linearly uncorrelated variables, namely the principal components. The principal components are arranged in descending order of their explained variance and provide a new basis to represent the data. Keeping the subset of the first m* PCs helps to provides a simpler representation of the data through dimensionality reduction while still retaining critical information. Here we rely on the fact, as pointed out by [44], that the highest variance principal components carry cohort-level functional connectivity information, while lower variance PCs carry finer subject-level functional connectivity information, and the lowest variance PCs carry information regarding noise and artifacts. By using the set of first m* PCs, which maximized averaged differential identifiability, for reconstruction provided a denoised version of the original FCs by keeping the cohort and finer subject level functional connectivity information.

To assess identifiability at a finer grain perspective, we considered the pairwise intraclass correlation coefficient (ICC) at the level of functional edges. Optimally reconstructed FCs systematically showed increased ICC values as compared to original FCs. At the meso-scale of looking at resting-state networks and their interactions, analogous ICC increases were found. In this study the groups were the test-retest visits within a site or between the two sites, whereas the measurements were the values of each func-
tional connectivity edge from all subjects. The reconstructed FCs represent a denoised version of the original data, having lower variance between measurements on different groups. ICC values in Figures 6-10 and Tables 2-3 indicated higher reproducibility of the functional connectivity profiles after optimal reconstruction. The reproducibility of the edges also helped to distinguish subjects and augment identifiability. In other words, higher ICC values led to higher identifiability of the functional connectivity edges. There was a notable increase in ICC values of the reconstructed data for the challenging problem of between-site test-retest visit pairs. Thus, the significant increase in ICC values for the reconstructed data denoted higher identifiability in all test-retest visit pairs for both NoGSR and GSR datasets after optimal reconstruction with $m^*$ PCs.

This work has several limitations. A limitation of the method is that this data-driven method requires the availability of test-retest sessions on all subjects and each site, which is usually not available in cross-sectional clinical studies. A limitation of the study is the modest sample size and small number of available sites. A larger multi-site study involving more subjects and sites will help to generalize the results. Further, better acquisition parameters for rs-fMRI may improve the results of the study.

This study expanded on the emerging field of fingerprinting in resting-state functional connectomes (FCs), by opening it to a less controlled scenario wherein repeated measurements are obtained from different imaging sites. To do so, it extended a recently proposed method to assess and ultimately improve identifiability in multi-site studies. Future studies could use this method to examine the reproducibility of fingerprinting in resting-state functional networks and structural connectivity across more than two sites. Another avenue of exploration would be to investigate the reliability of graph theory measures (e.g., clustering coefficient, characteristic path length, modularity, etc.) in the denoised FCs. Another important investigation would be to test the method presented in this study on scanners from different vendors, allowing combination of data for larger multi-site studies.

Multi-site fMRI studies have great appeal as a means of generating larger datasets, but the site-dependent variability can mask the advantages of such studies. Individual fingerprinting is a critical and emerging field in resting-state functional connectivity. Here we evaluated fingerprinting of the subjects in test-retest visit pairs, within and across two sites. We presented a framework based on principal component analysis to denoise the FCs and improve identifiability. We used principal components that maximized differential identifiability on the training data as an orthogonal basis to reconstruct subjects’ individual FCs for training and validation datasets. These optimally reconstructed FCs resulted in substantial improvement in individual fingerprinting within same-site visit pairs and also for the challenging problem of between-site visits, relative to the original data. Optimally reconstructed FCs systematically showed a notable increase in ICC values as compared to the original FCs, at the levels of functional edges, resting-state networks, and network interactions. Results showed that it is possible to use the data-driven method presented in this study to improve identifiability in the functional connectivity domain for multi-site studies. This would pave the way to pool subjects recruited at different sites, allowing for better assessments of brain structure and function in the healthy and diseased brain.

5 Compliance with Ethical Standards

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Purdue Discovery Park Data Science Award. The authors declare that they have no financial or non-financial conflicts of interest. All procedures performed in this study involving human participants were in accordance with the ethical standards of the Purdue Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants prior to participation in the study.

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