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# CONSTRUCTION OF MULTIMODAL CONNECTIONAL TEMPLATES OF BRAIN CORTICES FOR HEALTHY AND DISORDERED POPULATIONS

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## ABSTRACT

While several research methods were developed to estimate *individual-based* representations of brain connectional wiring (i.e., a connectome), traditionally captured using multimodal MRI data (e.g., functional and diffusion MRI), very limited works aimed to estimate brain *connectional template* for a *population* of connectomes. Estimating well-representative brain templates is a key step in data normalization and standardization for classification and group comparison studies. Recently, a pioneering framework was proposed to estimate a connectional template for a population of *unimodal* brain networks. However, estimating a connectional template for a population of *multimodal* brain connectomes lying on different manifolds is absent. Creating such a *multimodal brain connectional template* can leverage and integrate complementary multimodal connections from each imaging modality, which can facilitate the comprehensive investigation of how a specific disorder affects a population of patients. To fill this gap, we propose a cluster-based multi-view brain connectivity fusion framework to estimate a *connectional brain template* for a population of multimodal brain networks. Specifically, given a population of subjects, each with multimodal networks where each modality captures a brain connectional view, we first non-linearly fuse multimodal networks into a single fused network for each subject. Then, we cluster the fused networks to identify individuals sharing similar *fused* connectional traits in an unsupervised way. Next, through averaging networks in each cluster, we generate a representative connectional template. Finally, we construct the final multimodal connectional template by averaging the obtained template of all clusters. We evaluated our method on both healthy and disordered populations (with autism) and spotted differences between both connectional templates. Compared to other baseline methods, our fusion strategy achieved the best results in terms of template centeredness and representativeness.

***Index Terms—****brain morphological networks, cortex morphology, connectome, multimodal connectional template, graph fusion, disordered brain connectivity, MRI.*

## 1. INTRODUCTION

The study of brain connections has been widely developed for the last years thanks to the wealth of connectomic data collected through several projects including Human Connectome Project (HCP), Lifespan Baby Connectomes Project (BCP), and Connectome Related to Human Disease (CRHD).

Therefore, connectomic data estimated from structural (T1-w/T2-w), diffusion-weighted (DWI) and resting-state functional (rsFMI) magnetic resonance imaging (MRI) modalities is rapidly expanding. The richness of these multimodal connectional brain data can offer a powerful tool for better understanding of the human brain construct [ 1, 2], as well as capturing disordered brain alterations [3, 4]. However, the analysis of multimodal brain networks, which captures different views of the brain construct, is a relatively complicated task. Data fusion and concatenation techniques have been widely used to comprehensively integrate *individual-based* brain network from multiple brain views, where each brain view corresponds to an imaging modality. For instance, Wee *et al.* in [5], introduced a multiple-kernel Support Vector Machines to integrate information from structural and functional networks for mild cognitive impairment diagnosis. In recent works [6-8], morphological brain networks quantifying similarities between cortical regions were concatenated for dementia and autism diagnosis. However, to the best of our knowledge, all existing methods focus on fusing multimodal connectional information at the individual level —and not the *population* level.

Recently, Rekik *et al.* [9] introduced the concept of a *brain connectional template* (or *network atlas*), and proposed diffusive-shrinking graph technique to estimate a centered connectional template using a set of *unimodal* brain networks. However, this work was limited to investigating unimodal networks, encoding a single 'view of the brain'. Creating such a multimodal brain connectional template can leverage and integrate complementary aspects of multimodal connections derived from diverse imaging modalities, which can facilitate the comprehensive investigation of the effect of a given disorder on a population of patients. To fill this gap,

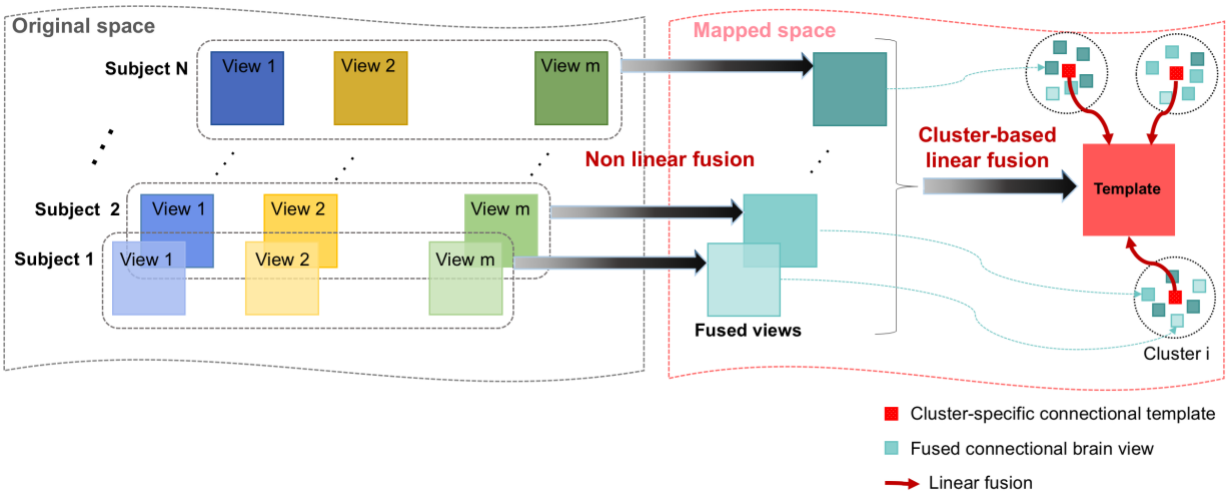


**Fig. 1.** *Illustration of the proposed multimodal brain connectional template estimation*. Give a population of $N$ subjects, each individual has $m$ brain connectional views. We first non-linearly fuse multimodal brain network views for each subject through graph-diffusion in the original space. Second, we cluster the fused views in the mapped space into $N_c$ clusters and produce a cluster-specific connectional template through linear fusion. Third, we estimate the final brain connectional template by averaging the $N_c$ cluster-specific templates.

we propose a cluster-based multi-view brain connectivity fusion framework to estimate a connectional brain template for a population of multimodal brain networks, which satisfies the following constraints: **1)** it is well centered (i.e., occupying a center position near to all views and all individuals), and **2)** it is well-representative of a specific population as it preserves shared traits across all individuals. Specifically, given a population of $N$ subjects, each with $m$ multimodal networks where each modality captures a brain connectional view, we first non-linearly fuse multimodal networks into a single fused network for each individual. Then, we cluster the fused networks to identify individuals sharing similar connectional traits in an unsupervised way. Next, through averaging networks in each cluster, we generate a representative connectional template. Finally, we construct the final multimodal connectional template by averaging the obtained representations of all clusters. Using our proposed method, we compare multimodal connectional templates estimated using a healthy population (normal controls —NC) and a disordered population diagnosed with Autism Spectrum Disorder (ASD).

## 2. PROPOSED METHOD

In this section, we detail each step of our proposed cluster-based multi-view brain connectivity fusion framework to estimate a connectional brain template for a population of multimodal brain networks. First, we model each unimodal brain network as a complete graph comprising $n$ nodes, where each node denotes an anatomical regions of interest (ROI) in the brain and the strength of each edge connecting two ROIs captures their similarity in a particular aspect (e.g., brain function or morphology). This can be mathematically defined as an $n \times n$ symmetric connectivity matrix $\mathbf{V}$, where each element $v_{ij} \in \boldsymbol{V}$ denotes the connectivity weight between two ROIs $i$ and $j$. A single brain connectivity between two ROIs can be measured using different MRI modalities. If one looks at each modality (e.g., rsfMRI) as capturing a single 'view' of the brain, then multiple brain imaging modalities can be leveraged to produce a *multi-view representation of the brain*. Hence, to develop an *effective* network fusion method for constructing a multimodal brain connectional template, one needs to well capture these multimodal connectional aspects.

Given a population of $N$ subjects, each subject $k$ is represented by a set of $m$ different brain network views $\{\boldsymbol{V_k^1}, \boldsymbol{V_k^2}, \ldots, \boldsymbol{V_k^m}\}$. Our goal is to estimate a multimodal connectional template that is well-centered (close to all views $\mathbf{V_k^v}$ and all $N$ subjects) and preserves shared multimodal connectional trends across individuals. **Fig.1** shows the three main steps of the proposed method.

**Individual-based non-linear fusion of connectional brain views (step 1).** For each subject in the population, different views of brain network might lie on different multimodal manifolds. A non-linear fusion function $\boldsymbol{\varphi}$ is then needed in order to derive a unique representative matrix $\boldsymbol{F_k}$ for the $m$ views as follows:

$$\boldsymbol{\varphi}(\{\boldsymbol{V_k^v}\}_{v=1}^{m}) \rightarrow \boldsymbol{F_k}$$

Basically, for each subject $k$, $\boldsymbol{\varphi}$ non-linearly maps the multi-view networks $\{\boldsymbol{V_k^v}\}_{v=1}^{m}$to a fused brain network $\boldsymbol{F_k}$ in the mapped or 'fusion' space. This allows to map all individuals to a common space where their brain views are unified individually. To do so, we leverage the generic similarity network fusion (SNF) developed by Wang et al. proposed in [10]. Specifically, we use SNF to define our mapping function $\boldsymbol{\varphi}$ in order to diffuse multi-view brain networks from the original space into the mapped space where they are fused. Given a subject $k$, for each connectivity matrix $\boldsymbol{V_k^v}, v \in$

$\{1, \dots, m\}$, we define a status matrix $\boldsymbol{P_k^v}$ that carries the full information about the connectivity weight of each ROI and a kernel matrix $\boldsymbol{S_k^v}$ that encodes the similarity to the $q$ nearest ROIs for each ROI. These matrices are initially defined as follows based on [9]:

$$P_k^v = \begin{cases} \frac{V_k^v(i,j)}{2\sum_{t\neq i} V_k^v(i,t)} & j \neq i \\ 1/2 & j = i \end{cases}; \; S_k^v = \begin{cases} \frac{V_k^v(i,j)}{\sum_{t\in N_i} V_k^v(i,t)} & j \neq i \\ 0 & otherwise \end{cases}$$

$N_i$ represents the set of $q$ neighbors of ROI $i$ using KNN algorithm. In order to integrate the different views into a single matrix, the status matrices $P_k^v$ are iteratively updated using this equation:

$$P_k^v = S_k^v \times \left(\frac{\sum_{t\neq v} P_k^t}{m-1}\right) \times (S_k^v)^T, v \in \{1, \dots, m\}$$

For each subject $k$ and view $v$, $P_k^v$ is iteratively updated through diffusing the global structure of other views $\left(\frac{\sum_{t\neq v} P_k^t}{m-1}\right)$ along the local sparse structure $S_k^v$ of the current view $v$. After $N_t$ iterations, we obtain the fused views of subject $k$ by averaging (i.e., fusing) the diffused status matrices $P_k^v$ at the final iteration $N_t$:

$$F_k = \frac{\sum_{v=1}^{m} P_k^v}{m}$$

The update of $P_k^v$ allows to iteratively integrate common as well as complementary information across brain networks during the fusion process.

**Fused network clustering in the mapped (fusion) space (step 2).** During non-linear fusion using SNF, weak connections within multimodal networks disappear and strong connections are added to one another. Therefore, network heterogeneous distribution present in the original space might persist in the mapped space. Hence, instead of directly fusing heterogeneous data samples in one step, we adopt a *hierarchical* merging step where we first identify individuals sharing similar connectional traits, then group them into more homogenous clusters in an unsupervised way. In this step, we use spectral clustering technique to cluster the fused networks $\{F_k\}_{k=1}^N$ in the mapped space into $N_c$ clusters. Spectral clustering is an effective tool for capturing global structure of graphs, so we start by constructing a similarity network between the fused views $F_k$, where the strength of each connection between two fused networks $F_i$ and $F_j$ is defined as the distance between the vectorized upper triangular parts of both matrices (as they are symmetric). Spectral clustering is then applied to obtain the final partition label vector $\boldsymbol{y}$, where $y_i$ denotes the label of the cluster to which the network $F_i$ belongs. This produces $N_c$ cluster-specific connectional templates for each cluster $c_i$ as follows:

$$\boldsymbol{F^{c_i}} = \frac{\sum_{k\in c} \boldsymbol{F_k}}{\boldsymbol{dim}(c_i)}$$

Where $\boldsymbol{dim}(c_i)$ denotes the number of elements in cluster $c_i$.

**Linear fusion (step 3).** After obtaining the cluster-based brain templates $\boldsymbol{F^{c_i}}_{i=1}^{N_c}$, we linearly average them into a single template denoting our multimodal connectional template as follows:

$$A = \frac{\sum \boldsymbol{F^{c_i}}}{N_c}$$

## 3. RESULTS AND DISCUSSION

### 3.1 Evaluation dataset and method parameters

We evaluated the proposed multimodal brain connectional template estimation framework on 341 subjects (186 ASD and 155 NC) from Autism Brain Imaging Data Exchange ABIDE I[1] public dataset, each with structural T1-w MR images. The average age (in years) for ASD subjects is 16.9 ranging from 8 to 38 and for NC subjects is 19.9 ranging from 8 to 39. The majority of subjects are males with a percentage of 90.32% in ASD population and 83.33% in NC population. We used FreeSurfer to reconstruct the left cortical hemisphere for each subject from T1-w MRI. Then, we parcellated it into 35 cortical regions using Desikan-Killiany Atlas. For each subject $S_k$, we generated $m = 4$ cortical morphological networks (4 views): $V_k^1$ denotes the maximum principal curvature brain view, $V_k^2$ denotes the mean cortical thickness brain view, $V_k^3$ denotes the mean sulcal depth brain view, and $V_k^4$ denotes the mean of average curvature.

For SNF parameters, the number of iterations is set to $N_t = 20$ as it guarantees SNF convergence [10]. We set the number of nearest neighbors to $q = 20$, and for the clustering we used $N_c = 5$ clusters for ASD dataset and $N_c = 6$ clusters for NC dataset using multi-fold cross-validation.

### 3.2 Method evaluation and comparison methods

To evaluate the centeredness of the estimated connectional cortical template, we used two distances: (1) the distance to the original space between the estimated template and each view of each subject, and (2) the distance to the mapped space between the estimated atlas and the fused views of each subject. The metric used for the evaluation is the mean Frobenius distance calculated as: $d_F(A,B) = \sqrt{\sum_i \sum_j |a_{ij} - b_{ij}|^2}$. A smaller distance indicates a more centered connectional template with respect to all individuals in the population and all views. The evaluation of the proposed method in comparison to baseline methods was validated using five randomized partitioning of data samples

[1] http://fcon 1000.projects.nitrc.org/indi/abide/

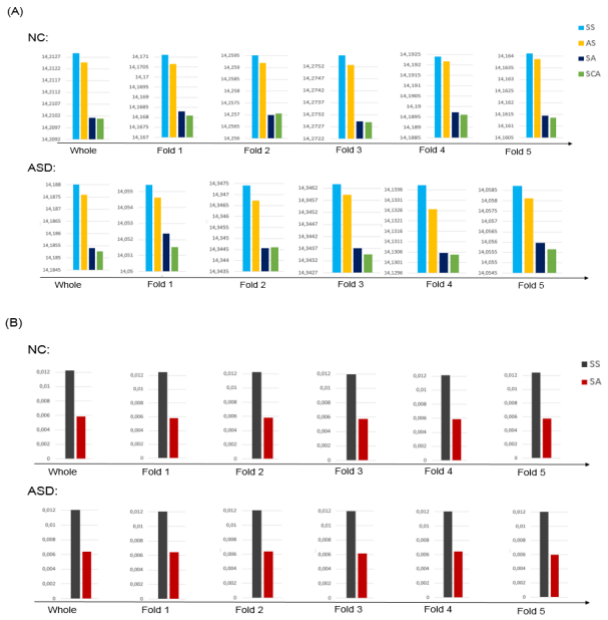


**Fig. 2.** Evaluation of the morphological multi-view brain network templates estimated for NC and ASD populations using different methods. (A) Distance of the estimated templates to views in the original space using SNF-SNF, average-SNF, SNF-average and SNF-clustering-average. (B) Distance to views in the mapped space of the estimated atlases using SNF-SNF and SNF-average.

using five-fold cross-validation, and tested using two populations of left hemisphere cortical brain networks: ASD and NC. We compared our proposed cluster-based network fusion (SCA) method to other baseline methods based on the adopted fusion techniques: (1) average-average (AA) method that first averages views for each subject, then average across subjects, (2) average-SNF (AS) first linearly averages views for each subject and then non-linearly fuses the obtained views using SNF, (3) the SNF-SNF (SS) technique which uses SNF to first fuse views for each subject, then merged all fused networks across subjects using SNF. Each of these distances is calculated in: (1) the original space (mean distance between the estimated template and the original views $\boldsymbol{V_k}$), and (2) the mapped space (mean distance between the estimated template and the fused views $\boldsymbol{F_k}$).

As shown in **Fig.2-A**, the proposed method (SCA) gave on average more centered connectional templates for both ASD and NC populations in the original space followed by Average-SNF, SNF-SNF, Average-Average and SNF-average methods. Average-average technique produced the highest template-to-population distance for ASD: 16.22 (average across folds), 16.05 (fold 1), 16.36 (fold 2), 16.42 (fold 3), 16.00 (fold 4), 16.26 (fold 5), and 16.39 (average across folds), 16.31 (fold 1), 16.44 (fold 2), 16.41 (fold 3), 16.40 (fold 4), 16.38 (fold 5) for NC respectively. We did not directly include this in **Fig.2-A** as they fall far away from the distance range of other methods. These results can be

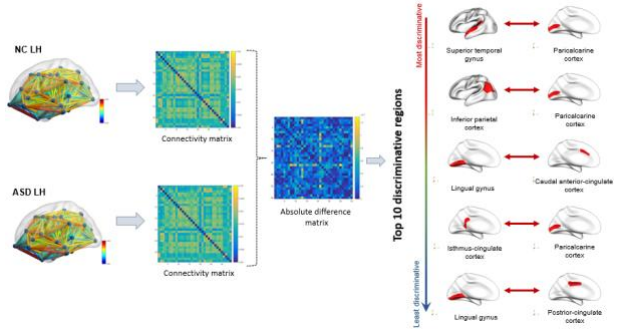


**Fig. 3.** Comparison between NC and ASD multimodal connectional templates and identification of top 5 discriminative connections between both templates.

explained by the fact that the different views of the brain networks lie on different manifolds, which requires a non-linear fusion technique in order to combine the multiple types of data. Therefore, we used the SNF technique in the *original* space to integrate the multiple views into a single connectivity network for each subject. The obtained fused networks then belong to the mapped space where they become all closer to one another through iterative diffusion (step 2). Hence, we used simple averaging as a linear fusion method to merge fused networks in the mapped space. Our method (SCA) had the best performance in terms of centeredness in the *original* space —especially for ASD population across all data partition folds. Besides, when evaluating the centeredness of the template in in the *mapped* space (**Fig.2-B**), SA remarkably outperformed SS while SCA caused a slight increase in the distance between the estimated template and the fused views (average across folds = 0.0067 for ASD and 0.0059 for NC). This might indicate that in the mapped space, one might need to use a different clustering method leveraging the properties of the fusion space to produce a more centered cluster-based template.

To identify multimodal connectional differences between ASD and NC templates, we identified the top 5 discriminative connections between both templates as shows in **Fig. 3.** Many regions were also associated with ASD in different studies [11-13] such as *anterior-cingulate cortex* responsible for the repetitive behavior in autistic subjects, *inferior parietal cortex* leading to attentional deficits, and *posterior cingulate cortex* responsible for the social impairment related to autism.

The proposed method had the best results in terms of centeredness in the original space compared to other baseline methods, yet it fell behind the proposed SA in terms of centeredness in the mapped space. In our future work, we will further refine this framework through leveraging advanced manifold learning and network clustering techniques [14] to generate centered connectional templates in both original and mapped spaces. In addition, we will build brain connectional templates for healthy individuals as well as patients with

other brain disorders (e.g., dementia) to better identify population-based distinctive changes in brain connectivity, thereby providing reliable features or biomarkers for an accurate diagnosis. Furthermore, building a multimodal brain connectional template that integrates morphological, functional and structural brain networks in a single reference template might help reveal how brain morphology relates to brain function and structure. Last, fusing connectional growth brain templates with connectional brain morphology templates might give us unprecedented insights into the rate at which a disorder progresses and affects the morphology of a pair or set of anatomical regions [15].

## 4. CONCLUSION

In this work, we unprecedentedly proposed a *population-based* multimodal network fusion framework for estimating a multimodal connectional brain template for both healthy and disordered populations. Our method had the best results in terms of centeredness when tested on morphological brain networks, yet it can be applied to all types of brain networks (e.g., structural or function). Building multimodal brain connectional templates can be utilized as 'references' to normalize individual brain networks for comparative studies. In our future work, we will explore multi-manifold learning methods for nesting brain views, which will eventually produce more robust clustering results to outliers in both original and mapped spaces.

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