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Concurrent brain parcellation and connectivity estimation via co-clustering of resting state fMRI data: A novel approach

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Abstract

Connectional topography mapping has been gaining widespread attention in human brain imaging studies. However, existing methods might not effectively utilize the information from neuroimaging data, thus hindering the understanding of the underlying connectional organization in the brain and uncovering the optimal clustering number from the data. In this study, we propose a novel method for the automated construction of inherent functional connectivity topography in a data-driven manner by leveraging the power of co-clustering-based on resting state fMRI (rs-fMRI) data. We propose the co-clustering-based method not only for concurrently parcellating two interconnected brain regions of interest (ROIs) under consideration into functionally homogenous subregions, but also for estimating the connectivity between these subregions from the two brain ROIs. In particular, we first model the connectional topography mapping as a co-clustering-based bipartite graph partitioning problem for constructing the inherent functional connectivity topography between the two interconnected brain ROIs. We also adopt an objective criterion, that is, silhouette width index measuring clustering quality, for determining the optimal number of clusters. The proposed method has been validated for mapping thalamocortical connectional topography based on rs-fMRI data of 57 subjects. Validation results have demonstrated that our method identified the optimal solution with five pairs of mutually connected subregions of the thalamocortical system from the rs-fMRI data, and could yield more meaningful, interpretable, and homogenous connectional topography than existing methods. The proposed method was further validated by the high symmetry of the mapped connectional topography between two hemispheres.

KEYWORDS
co-clustering, fMRI, functional connectivity, connectional topography mapping, thalamocortical

1 | INTRODUCTION

Connectional topography plays important role in brain functions and behaviors, and can provide insight into neurodevelopment, too (Phillips, Fish, Kambi, Redinbaugh, & Saalmann, 2019; Thompson, Mohammadi-Nejad, Robinson, Andersson, & Sotiropoulos, 2020; Wu, Calhoun, Jung, & Caprihan, 2015). Many neuropsychiatric disorders, such as schizophrenia, have been manifested by disrupted communications for connections between distributed brain networks (Gong et al., 2019; Jiang et al., 2019; Kim et al., 2020; Rolls et al., 2020; Sheffield, Rogers, Blackford, Heckers, & Woodward, 2020). Thus, connectional topography mapping is a matter of utmost importance for revealing the connectional organization of the brain. However, the connectional topography mapping is a more sophisticated analysis than conventional region-of-interest or voxel-based morphometry analysis, as the connectional analysis is required to clarify the interregional or intervoxel relationships (Wu et al., 2015).

In recent decades, neuroimaging techniques, especially functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), have become increasingly important for unveiling the connectional organization in the human brain, which is essential for noninvasively exploring human brain functions (Mars, Passingham, & Jbabdi, 2018). With plenty of connectivity information provided by the neuroimaging data, numerous methods have been proposed for connectional topography mapping of the human brain (Behrens et al., 2003; Hwang, Bertolero, Liu, & D'Esposito, 2017; Jiang et al., 2019; Johansen-Berg et al., 2005; O'Muircheartaigh et al., 2011; O'muircheartaigh & Jbabdi, 2018; O'muircheartaigh, Keller, Barker, & Richardson, 2015; Wu et al., 2015; Wu, Caprihan, Bustillo, Mayer, & Calhoun, 2018; Yuan et al., 2016; Zhang et al., 2008; Zhang, Snyder, Shimony, Fox, & Raichle, 2010).

Existing connectional topography mapping methods can be divided into three main categories, that is, prior connectivity based mapping method (Behrens et al., 2003; Hwang et al., 2017; Jiang et al., 2019; Johansen-Berg et al., 2005; Zhang et al., 2008, 2010), independent component analysis (ICA) based mapping method (O'Muircheartaigh et al., 2011; O'muircheartaigh et al., 2015; O'muircheartaigh & Jbabdi, 2018; Wu et al., 2015, 2018; Yuan et al., 2016), and clustering-based mapping method (Guevara, Román, Houenou, Duclap, & Guevara, 2016; Heuvel & Pol, 2010; Lee et al., 2012; Salehi, Karbasi, Shen, Scheinost, & Constable, 2018; Toro-Serey, Tobyne, & McGuire, 2020; Van Den Heuvel, Mandl, & Pol, 2008; Yeo et al., 2011). In particular, the prior connectivity based mapping method is a hypothesis-driven approach, which needs prior knowledge (i.e., prior brain targets) for mapping connectional topography. The prior brain targets are usually obtained from anatomical/cytoarchitectural templates (Behrens et al., 2003; Johansen-Berg et al., 2005; Zhang et al., 2008, 2010), or structural/functional brain parcellations (Hwang et al., 2017; Jiang et al., 2019). This kind of mapping method assigns each voxel within one brain region of interest (ROI), considered for mapping its connectional topography, to one of the prior brain targets that has the strongest connectivity strength with that voxel based on fMRI data (Hwang et al., 2017; Jiang et al., 2019; Zhang et al.,

2008, 2010), or DTI data (Behrens et al., 2003; Hwang et al., 2017; Johansen-Berg et al., 2005; Zhang et al., 2010). The identified subregions and their respective connected brain targets compose the constructed connectional topography.

Additionally, the ICA based mapping method is a data-driven approach, which can construct meaningful connectional topography of a certain neural circuit in consideration by applying ICA to functional connectivity profiles derived from fMRI data (Wu et al., 2018; Yuan et al., 2016), or structural connectivity profiles derived from DTI data (O'Muircheartaigh et al., 2011; O'muircheartaigh et al., 2015; O'muircheartaigh & Jbabdi, 2018; Wu et al., 2015). This kind of mapping method usually constructs the connectional topography at the whole-brain level, which is generally achieved by applying ICA to connectivity profiles (O'Muircheartaigh et al., 2011; O'muircheartaigh et al., 2015; O'muircheartaigh & Jbabdi, 2018; Wu et al., 2015, 2018; Yuan et al., 2016).

Besides the ICA based mapping method, the clustering-based mapping method is a data-driven approach as well, which is also able to construct meaningful connectional topography in the human brain by clustering functional connectivity profiles derived from fMRI data (Heuvel & Pol, 2010; Lee et al., 2012; Salehi et al., 2018; Toro-Serey et al., 2020; Van Den Heuvel et al., 2008; Yeo et al., 2011), or structural connectivity profiles derived from DTI data (Guevara et al., 2016). The existing clustering-based mapping method commonly constructs the connectional topography at the whole-brain level similar to the ICA based mapping method, which is typically achieved by grouping connectivity profiles utilizing clustering algorithms, such as normalized cut (Toro-Serey et al., 2020; Van Den Heuvel et al., 2008).

Overall, the ICA and existing clustering-based mapping methods have shown their superiority for constructing more meaningful connectional topography than the prior connectivity based mapping method. The main reason for this is that the ICA and clustering-based mapping methods are both data-driven approaches, which are not dependent on prior knowledge as the hypothesis-driven method (i.e., the prior connectivity based mapping method). However, both ICA based mapping method and the existing clustering-based mapping method are not sufficiently suitable for constructing fine-grained connectional topography of a certain neural circuit in consideration. Furthermore, the determination of the optimal granularity from data in connectional topography mapping for the existing hypothesis-driven and data-driven methods remains a major challenge.

To address the aforementioned challenges, we propose a novel method for automatically constructing inherent connectional topography from resting state fMRI (rs-fMRI) data in a data-driven manner, by leveraging the co-clustering-based bipartite graph partitioning. Specifically, the novel connectional topography mapping method is first proposed for simultaneously identifying subregions of one brain ROI and their respective connected subregions of another brain ROI (i.e., the first brain ROI's interconnected brain structure) via co-clustering based on rs-fMRI data. The identified subregions and their respective connected subregions compose the mapped connectional topography

between the two brain ROIs. Then, modified silhouette width (SI) index measuring clustering quality is adopted as an objective criterion to determine the optimal number of pairs of mutually connected subregions between the two brain ROIs (Cheng, Wu, & Fan, 2014; Cheng, Zhu, Zheng, Liu, & He, 2020; Craddock, James, Holtzheimer III, Hu, & Mayberg, 2012).

We have validated the proposed method for mapping connectional topography of the thalamocortical system based on 57 subjects' rs-fMRI data obtained from Beijing Normal University 1 (BNU 1) (Lin et al., 2015). Validation results have demonstrated that the mapped five-cluster connectional topography with the proposed method was the optimal solution according to the objective clustering quality criterion. More importantly, the proposed method could construct more meaningful, interpretable, and homogeneous connectional topography compared with existing methods. The validity of the proposed method was further verified by the high symmetry of the mapped connectional topography between two hemispheres.

2 | MATERIALS AND METHODS

2.1 | The novel co-clustering method for connectional topography mapping

The proposed method is a novel co-clustering approach for automatically mapping connectional topography of the human brain based on rs-fMRI data in a data-driven manner. The proposed co-clustering based mapping method is comprises three key steps (Figure 1). Firstly, two brain regions of interest (ROIs), from a certain neural circuit under consideration, are extracted for mapping their connectional topography (Figure 1a). Generally, one brain ROI is a subcortical brain structure, and the other brain ROI is the brain cortex interconnected with the subcortical brain structure. Secondly, a functional similarity matrix is formed with dimensions $n_r \times n_c$ between the extracted two brain ROIs, where n_r and n_c are the number of voxels in the two brain ROIs, respectively (Figure 1b). The matrix element, that is, functional similarity, is computed on the basis of the functional connectivity between rs-fMRI signals. Simultaneously, a corresponding bipartite graph model of the functional similarity matrix is established for connectional topography mapping via co-clustering. Finally, the established bipartite graph is co-partitioned by utilizing the co-clustering for mapping connectional topography between the two brain ROIs (Figure 1c).

2.1.1 | Extracting brain regions of interest

To precisely extract brain ROIs, two brain ROIs, that is, two interconnected brain structures, are extracted from subjects' structural magnetic resonance imaging (sMRI) data other than frequently used brain templates. Particularly, for each subject s_i, i = 1, 2, ..., N in a data set, the subcortical structures and cerebral cortex are segmented from their sMRI data using FreeSurfer (Fischl et al., 2002). As an example, Figure 1a shows the obtained substructure thalamus and its interconnected brain cortex of a randomly selected subject.

2.1.2 | Modeling bipartite graph for co-clustering

In the proposed method, the spectral co-clustering algorithm is adopted for mapping the connectional topography (Dhillon, 2001; Huang, Xu, Tsang, & Kang, 2020). This proposed co-clustering based
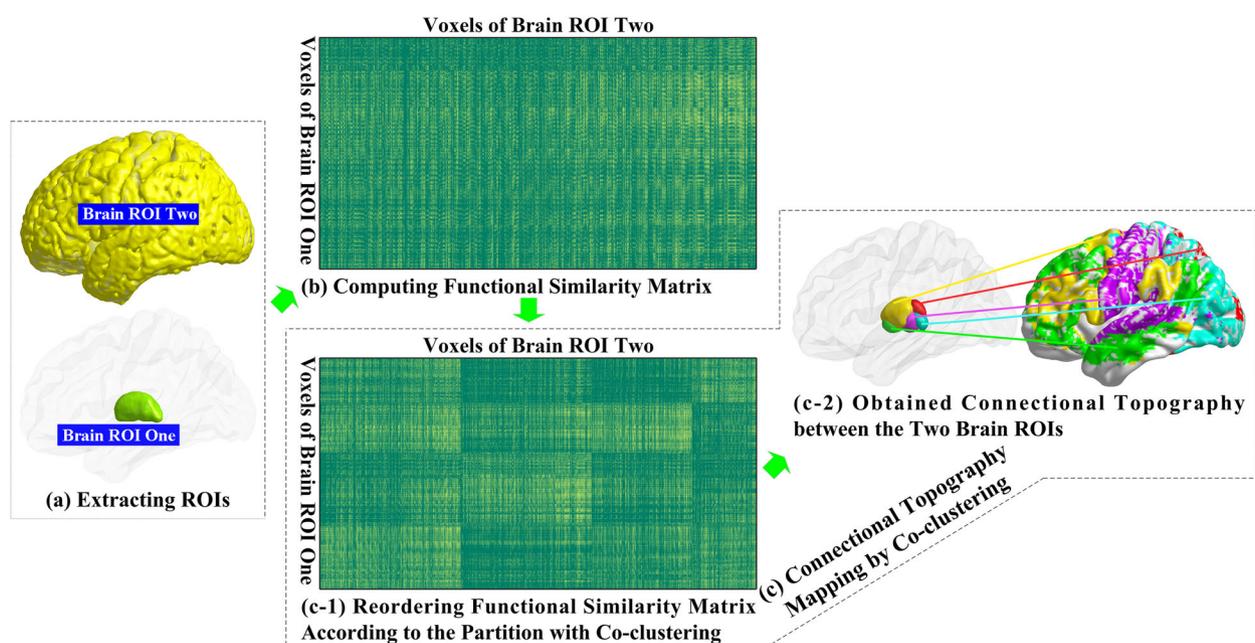
FIGURE 1 Framework of the proposed connectional topography mapping method. Abbreviation: ROIs, regions of interest

connectional topography mapping method is firstly required to build bipartite graph model $G_d = (V_r, V_c, \varepsilon_d)$, and simultaneously compute functional similarity matrix M_g between two brain ROIs of a certain neural circuit under consideration. Here, the bipartite graph is constructed by modeling all voxels in each of the two brain ROIs as graph nodes $V_r = \{u_i \mid i = 1, 2, ..., n_r, n_r = |V_r|\}$ and $V_c = \{v_i \mid i = 1, 2, ..., n_c, n_c = |V_c|\}$, respectively ($|\cdot|$ is the cardinality of a set), and by connecting each pair of voxels from the two different brain ROIs as graph edges $\varepsilon_d = \{\langle u, v \rangle \mid u \in V_r, v \in V_c\}$. The graph edge weights $\{m_g(u, v) \mid u \in V_r, v \in V_c\}$ constitute the functional similarity matrix $M_g \in \mathbb{R}^{n_r \times n_c}$.

In this study, a graph edge weight is defined by measuring the functional similarity of functional signals. Generally, the functional similarity is defined based on the functional connectivity measure between functional signals, that is, Pearson correlation coefficient (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995)

$$r(u,v) = \frac{(1/T)\sum_{t=1}^{T}\left(I(u,t)-\bar{I}(u)\right)\left(I(v,t)-\bar{I}(v)\right)}{S_I(u)S_I(v)} \quad (1)$$

where $u \in V_r$, $v \in V_c$, $I(u, t)$, and $I(v, t)$ are functional signals of voxels u and v at time point t, T is the number of time points, $\bar{I}(\cdot) = (1/T)\sum_{t=1}^{T}I(\cdot,t)$ and $S_I(\cdot) = \sqrt{1/(T-1)\sum_{t=1}^{T}\left(I(\cdot,t)-\bar{I}(\cdot)\right)^2}$ are mean and SD of functional signals, respectively.

Due to the low signal-to-noise ratio (SNR) of functional signals, it is difficult to construct robust connectional topography by directly utilizing the functional connectivity measure as graph edge weight (Luo et al., 2020). In order to overcome the noise of functional signals, a one-sample t test is firstly applied to functional connectivity measures from a group of subjects, and the resulting t-statistic value is adopted as a functional similarity measure for mapping robust connectional topography of the human brain at the group level (Zhang & Li, 2014). In addition, the bipartite graph model requires graph edge weights to be nonnegative, whose optimal solution can be computed efficiently by solving an eigenvalue problem (Dhillon, 2001; Huang et al., 2020). Moreover, providing that the functional similarity measure between two voxels is negative, the two voxels are most likely to belong to two different functional networks (Fox et al., 2005). Therefore, for a given data set with N subjects s_i, $i = 1, 2, ..., N$, the graph edge weight, that is, functional similarity here, based on the t-statistic value of the functional connectivity measures from the N subjects can be defined as

$$m_g(u,v) = \begin{cases} \frac{\bar{r}(u,v)-\mu}{s(u,v)/\sqrt{N}} & \text{if } \frac{\bar{r}(u,v)-\mu}{s(u,v)/\sqrt{N}} > 0, \\ 0 & \text{otherwise} \end{cases} \quad (2)$$

where $u \in V_r$, $v \in V_c$, $\mu = 0$, $\bar{r}(u,v) = 1/N\sum_{i=1}^{N}r_{s_i}(u,v)$ and $s(u,v) = \sqrt{1/(N-1)\sum_{i=1}^{N}(r_{s_i}(u,v)-\bar{r}(u,v))^2}$ are mean and SD computed from functional connectivity measures of the N subjects, respectively, $r_{s_i}(u,v)$ is the functional connectivity measure between voxels u and v for subject s_i. The defined graph edge weights $\{m_g(u, v)\} \mid u \in V_r, v \in V_c\}$ constitute the functional similarity matrix M_g at the group level. The diagram of the heat map for the functional similarity matrix M_g is shown in Figure 1b.

2.1.3 | Co-partitioning bipartite graph for connectional topography mapping

The constructed bipartite graph model $G_d = (V_r, V_c, \varepsilon_d)$ is solved by the spectral co-clustering algorithm for connectional topography mapping (Cheng, Liu, & Tao, 2019). In particular, the established bipartite graph model can be firstly viewed as an undirected weighted graph model $G_o = (V, A_g, \varepsilon_o)$. This undirected weighted graph $G_o = (V, A_g, \varepsilon_o)$ is constructed by modeling all voxels from the two brain ROIs as graph nodes $V = V_r + V_c$, and connecting each pair of graph nodes from V consisting of graph edges $\varepsilon_o = \{\langle u, v \rangle \mid u, v \in V\}$, and the number of graph nodes V is $n = n_r + n_c$. The graph edge weights $\{a_g(u, v) \mid u, v \in V\}$ constitute an affinity matrix, which is defined as (Dhillon, 2001)

$$A_g = \begin{bmatrix} 0 & M_g \\ M_g^T & 0 \end{bmatrix}, \quad (3)$$

where $\cdot^T$ denotes the transpose of a matrix, M_g is the functional similarity matrix, and $A_g \in \mathbb{R}^{n \times n}$ is a symmetric block matrix.

Subsequently, the bipartite graph co-clustering problem is transformed into a spectral partitioning problem. Suppose the undirected weighted graph G_o is partitioned into k clusters $V = \{V_1, V_2, ..., V_k\}$, and the objective function of normalized cut on the undirected weighted graph $G_o = (V, A_g, \varepsilon_o)$ is defined as follows (Shi & Malik, 2000)

$$Ncut(G_o) = \min_{V_1, V_2, ..., V_k} \sum_{i=1}^{k} \frac{cut(V_i, V-V_i)}{assoc(V_i, V)}, \quad (4)$$

where $assoc(V_i, V) = \sum_{u \in V_i, v \in V} a_g(u,v)$, $cut(V_i, V-V_i) = \sum_{u \in V_i, v \in V-V_i} a_g(u,v)$, and $a_g(u, v)$ is the value of an element of the affinity matrix A_g at the location (u, v). Based on the k-cluster partition $V = \{V_1, V_2, ..., V_k\}$, the two brain ROIs is correspondingly partitioned into k pairs of mutually connected subregions. In detail, for each pair of the mutually connected subregions, one subregion is partitioned from one brain ROI, and the other subregion is partitioned from the other brain ROI.

These pair-wisely connected subregions form the connectional topography between the two brain ROIs of a certain neural circuit under consideration. The co-clustering based connectional topography mapping is intuitively achieved through simultaneously clustering columns and rows of the functional similarity matrix M_g. Figure 1(c-1) is the reordered functional similarity matrix according to the partition with co-clustering, showing that the reordered functional similarity matrix has clearly identifiable clusters in both column and row directions. In addition, Figure 1(c-2) shows the diagram of the constructed thalamocortical connectional topography with the proposed method.

2.2 | Objective criterion for determining the optimal number of clusters

In our proposed method, the clustering number must be known in advance in order to construct the connectional topography via the co-clustering. In the current study, an objective criterion is adopted to

determine the optimal clustering number. The following criterion defines the clustering quality of the mapped connectional topography. In particular, the modified SI index is a clustering quality measure, which is used as the objective criterion to identify the optimal clustering number from rs-fMRI data and to quantify the functional homogeneity of mapped connectional topography. The modified SI index for a given mapped connectional topography is defined as (Cheng et al., 2014, 2020; Craddock et al., 2012)

$$SI = \frac{1}{k}\sum_{i=1}^{k}\frac{a_i - b_i}{\max\{a_i, b_i\}}, \tag{5}$$

where k is the number of pair-wisely connected subregions, $a_i = (1/(n_i(n_i-1)))\sum_{u,v\in V_i, u\neq v} a_g(u,v)$ is the average functional affinity measures between every pair of voxels u and v assigned to i^{th} pair-wisely connected subregions V_i, $b_i = (1/(n_i(n-n_i))\sum_{u\in V_i}\sum_{v\notin V_i} a_g(u,v)$ is the average functional affinity measures between voxel u in V_i and voxel v in $V - V_i$. The $a_g(u, v)$ is the element of the affinity matrix A_g defined in Equation (3), n_i is the number of voxels of the ith pair-wisely connected subregions V_i, n is the number of graph nodes V considered for constructing the connectional topography.

The optimal clustering number k^* is selected, when the SI value of the mapped connectional topography is the largest among $k = 2, 3, ...,$ and K cluster solutions (Rousseeuw, 1987). The maximum clustering number K is chosen according to the spatial resolution of rs-fMRI data, guaranteeing that the K is sufficiently large.

2.3 | Validation analysis

The proposed method is validated for constructing the connectional topography of the thalamocortical system based on 57 subjects' rs-fMRI data. Firstly, the data set and preprocessing are described. In addition, the validity of the proposed method is assessed by measuring the symmetry of the mapped connectional topography. Furthermore, the superiority of the proposed method is evaluated by comparing with existing methods in terms of functional homogeneity.

2.3.1 | Data set and preprocessing

The proposed method has been validated for mapping thalamocortical connectional topography within each hemisphere based on rs-fMRI data. In particular, 57 healthy subjects' fMRI data from BNU 1 data set was used in the current study, and there are 30 males and 27 females in the data set (age: 23.05±2.29, age range: 19–30) (Lin et al., 2015). For each subject, the fMRI data have a spatial resolution of $3.125 \times 3.125 \times 4.2$ mm^3, consisting of 200 time points at repetition time (TR)=2 s. Structural MRI data from the BNU 1 data set was also used to extract the substructure thalamus and its interconnected brain cortex for mapping connectional topography of the thalamocortical system in the current study (Figure 1a). The structural MRI data of each subject has a spatial resolution of $1 \times 1 \times 1.33$ mm^3,

which was used to assist rs-fMRI data preprocessing as well. In our experiments, the maximum clustering number K was set to 10, taking into account that the fMRI has relatively low spatial resolution. The imaging protocol was approved by the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, and written informed consent was obtained from all subjects (Lin et al., 2015).

The rs-fMRI data were preprocessed with the following steps: (a) discarding the first five time points to allow for equilibrium magnetization; (b) 3D rigid-body head motion correction to the middle frame of data; (c) global 4D intensity normalization to a whole-brain mean value of 10,000; (d) nonlinear registration to Montreal Neurological Institute (MNI)-152 template with spatial resolution $3 \times 3 \times 3$ mm^3 based on the deformation field obtained from their co-registered sMRI data using DARTEL as implemented in SPM12; (e) spatially smoothing with a 6 mm full width at half-maximum (FWHM) Gaussian kernel; (f) removal of motion artifacts with ICA-based Automatic Removal of Motion Artifacts (ICA-AROMA) (Pruim, Mennes, Buitelaar, & Beckmann, 2015); (g) regression out of a set of nuisance signals including signal averaged over the white matter, signal-averaged over the cerebrospinal fluid, and linear and quadratic trends; (h) temporally high-pass filtering (cutoff frequency of 0.01 Hz). The preprocessing procedures were performed by using tools from the Statistical Parametric Mapping software (SPM12 version 7,487; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). In particular, the sMRI images were segmented into white matter, gray matter, and cerebrospinal fluid by using new segmentation for extracting physiological nuisance signals for regression, that is, average signals from white matter and cerebrospinal fluid (Ashburner et al., 2014).

2.3.2 | Assessment of consistency in estimated connectivity

To examine the consistency in estimated connectivity, post hoc functional connectivity analysis is carried out for the mapped connectional topography at a group level. In particular, the functional connectivity, measured by Pearson correlation coefficient r, is firstly computed as in Equation (1) between mean functional signals within each pair of identified thalamic and cortical subregions from the mapped connectional topography (Biswal et al., 1995). Next, the Pearson correlation coefficient r is converted into z value by using Fisher's transform to improve the normality of the coefficient's distribution calculated by $z = \frac{1}{2}\log\frac{1+r}{1-r}$ (Zar, 1999). Then, one sample t test is applied to the standardized functional connectivity measures, that is, transformed z values, between each thalamic subregion and each cortical subregion from the mapped connectional topography across all subjects in a data set. Finally, the t value of the statistics is transformed into z value, and the functional connectivity with statistical significant is determined at $p < .05$ using family-wise error (FWE) correction for multiple comparisons. The resulting statistically significant functional connectivity with the top-three largest z values for each subregion is referred as group-level functional connectivity.

2.3.3 | Symmetry index for mapped connectional topography

To evaluate the validity of the proposed method, an index is adopted to quantify the symmetry in the mapped connectional topography between two hemispheres. For each of the pair-wisely connected subregions, the symmetry measure is computed by (Kahnt, Chang, Park, Heinzle, & Haynes, 2012)

$$SI_i = \frac{1}{n_i}\sum_{u \in V_i}\begin{cases} 1 & if \ l_u = l_{u'} \\ 0 & otherwise \end{cases} \tag{6}$$

where $i = 1, 2, ..., k^*$, n_i is the number of voxels of the ith pair-wisely connected subregions V_i from one hemisphere, u' is the mirrored voxel of u from the other hemisphere, and $l.$ denotes a voxel's subregion label.

2.3.4 | Competitive connectional topography mapping approaches

In addition to the proposed co-clustering based group-wise connectional topography mapping method, there are three other prior connectivity, ICA and clustering-based mapping approaches that have been presented to construct the connectional topography of the brain at the group level. In the first approach, a substructure (i.e., thalamus here) considered for mapping its connectional topography is parcellated into subregions by assigning each voxel of the substructure to one of the prior defined brain targets with the strongest group-level functional connectivity (Hwang et al., 2017; Jiang et al., 2019; Zhang et al., 2008, 2010). In our experiments, five cortical regions were selected as brain targets in the prior connectivity based mapping approach, which are prefrontal zone, temporal zone, primary motor/premotor zone, somatosensory zone, and posterior parietal/occipital zone (Zhang et al., 2008, 2010). In addition, the group-level functional connectivity strength between the substructure's voxels and the brain targets was measured by using t value calculated following the Subsection 2.3.2.

In the second approach, the ICA is applied to the functional similarity matrix between two brain ROIs of a certain neural circuit (i.e., thalamocortical system here) considered for connectional topography mapping (Wu et al., 2018). The group-level functional similarity matrix M_g for the thalamocortical system calculated as described in the Subsection 2.1.2 is firstly decomposed into mutually linked independent components (ICs) by means of ICA, and the number of pairs of decomposed mutually linked ICs is set to the optimal clustering number k^* determined in our proposed co-clustering based mapping method. Then, each voxel within the thalamocortical system is assigned to one IC based on its maximum z score among the decomposed k^* ICs by means of the winner-take-all (WTA) rule. The resulting WTA map is the constructed connectional topography of the thalamocortical system at the group level with the ICA based mapping approach.

In the third approach, many clustering algorithms are adopted to construct the connectional topography of the brain, and the normalized cut is one of the excellent clustering algorithms (Heuvel & Pol, 2010; Lee et al., 2012; Salehi et al., 2018; Toro-Serey et al., 2020; Van Den Heuvel et al., 2008; Yeo et al., 2011). So, the normalized cut based mapping method is chosen as a representative approach for comparison, which is a two-level mapping approach. The two-level normalized cut based mapping method can construct more robust and accurate group-level connectional topography than the connectional topography identified by applying a clustering approach (such as a normalized cut) to group-level functional connectivity (Van Den Heuvel et al., 2008). The normalized cut based mapping method firstly constructs the connectional topography at the individual level. Then, this method constructs the group-level connectional topography through clustering the consistency of resulting individual connectional topographies across all subjects in a group, and the constructed group-level connectional topography is chosen for comparison. Particularly, the normalized cut is applied to each subject's Pearson correlation matrix of the brain region (i.e., thalamocortical system here) considered for parcellation after thresholding (cutoff threshold 0.4), and the matrix element (i.e., the Pearson correlation coefficient between functional signals) is calculated according to Equation (1). The partitions from each subject are utilized to calculate a group-level weight matrix as follows. For each element of the weight matrix, the number of subjects is counted when two voxels from the thalamocortical system have the same partitioning label. This number is divided by the total number of subjects in a group, and the ratio is adopted as the value for the element of the weight matrix. Mathematically, the value of the element in the weight matrix is defined as

$$w(u,v) = \frac{1}{N}\sum_{S_i, i \in \{1,2,...,N\}} count_{S_i}(u,v), \tag{7}$$

where S_i is one of the N subjects in a data set, $count_{S_i}(u,v)$ is equal to 1 if voxels u and v have the same partitioning label in subject S_i and 0 otherwise. Then, the normalized cut is applied to the group-level weight matrix for parcellation of the thalamocortical system. The final partition is the constructed connectional topography of the thalamocortical system at the group level with the normalized cut based mapping approach. For both individual and group partitions, the clustering number is set to the optimal clustering number k^* determined in our proposed co-clustering based mapping method.

To evaluate the proposed method's quality, the proposed method is compared quantitatively to the three alternative methods with their aforementioned parameter settings. In particular, the proposed method and the three alternative methods firstly construct the connectional topography at the group level. Then, the modified SI index defined in Equation (5) is used to measure the functional homogeneity of the mapped connectional topographies obtained by these methods, respectively. Finally, the proposed method and the three alternative methods are compared with respect to the functional homogeneity measured by the modified SI index. The SI value is in the range $(-\infty, +\infty)$. When the mapped connectional topography is an

incorrect partition, the SI value is negative, and if the mapped connectional topography is a good partition, the SI value is near 1.

3 | RESULTS

3.1 | Mapped connectional topography by the proposed method

The modified SI index, measuring the clustering quality of mapped connectional topography, was adopted as the objective criterion for selecting the optimal clustering number in our proposed method. Figure 2 exhibits that five-cluster solution has the global maximum SI value among $k = 2, 3, ...,$ and K cluster solutions, thus $k^* = 5$ was selected as the optimal clustering number.

Subsequently, Figure 3 presents the mapped connectional topographies of bilateral thalamocortical systems with five-cluster solution. As shown in Figure 3, the human thalamocortical system could be successfully co-partitioned into five pairs of mutually connected subregions based on rs-fMRI data by the proposed method. In particular, all of the five cortical subregions are well-studied brain networks, which are frontoparietal network, default mode network, visual network, sensorimotor network, and precuneus network, respectively. Correspondingly, the five co-partitioned thalamic subregions are named frontoparietal area, default mode area, visual area, sensorimotor area, and precuneus area, respectively according to their respective connected cortical networks. Since mutually connected brain regions should have close functional associations, the brain functions of co-partitioned thalamic subregions could be inferred from their respective connected well-studied cortical networks. These results have indicated that the proposed method could construct neurobiologically meaningful and interpretable connectional topography.

In post hoc analysis, the thalamic and cortical subregions from the constructed connectional topography show significant functional connectivity at group level. As shown in Figure 4, the top-three most significant functional connections for each subregion contain the connection estimated by our proposed method. This is to say that functional connections obtained by post hoc analysis are almost consistent with the connections of mutually connected subregions from the mapped connectional topography.

3.2 | Symmetry of the mapped connectional topography

The mapped connectional topography of the thalamocortical system has high symmetry, which is illustrated by symmetry measures for each of the pair-wisely connected subregions between two hemispheres shown in Figure 5. Particularly, the symmetry measures are 0.80, 0.93, 0.69, 0.68, and 0.20 for the frontoparietal area with the frontoparietal network, default mode area with default mode network, visual area with visual network, the sensorimotor area with the sensorimotor network, and precuneus area with precuneus network, respectively. The fifth pair-wisely connected subregions, that is, precuneus area with precuneus network, has lower symmetry, which might be more vulnerable to the noise in the rs-fMRI data. In general, these results have demonstrated that the mapped connectional topography is fairly similar between two hemispheres. This evaluation provides sufficient face validity for the proposed co-clustering based connectional topography mapping method.

3.3 | Comparison with existing methods

The proposed method was compared both qualitatively and quantitatively with existing methods. Qualitatively, the proposed method does not depend on prior knowledge, so that the mapped connectional topography with our method would not be biased towards prior brain targets required by the prior connectivity based mapping method. More specifically, the prior connectivity based mapping method usually use the following anatomically defined cortical regions, including prefrontal zone, temporal zone, primary motor/premotor zone,
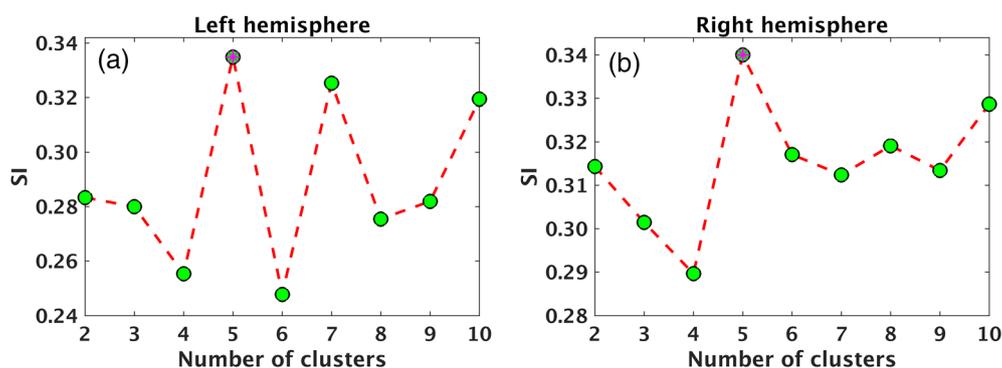
FIGURE 2 Determination of optimal clustering number in the proposed method based on clustering quality measured by modified SI index. (a) and (b) SI value for the mapped connectional topographies of bilateral thalamocortical systems with the proposed method as a function of k ($k = 2, 3, ..., 10$), respectively. The SI values of five-cluster solutions for both left and right hemispheres are maximal, suggesting that the optimal clustering number is five. Abbreviation: SI, silhouette width
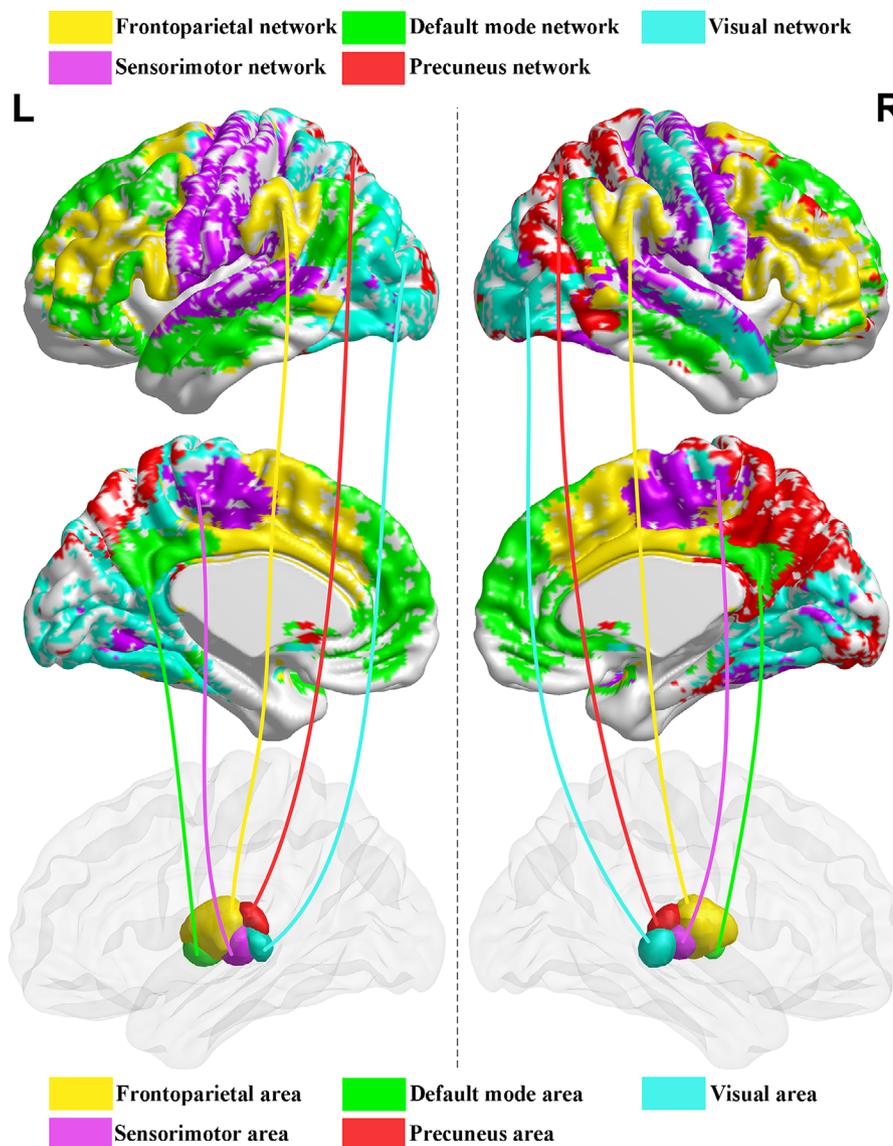
FIGURE 3 The thalamocortical connectional topography of the optimal solution with five pairs of mutually connected subregions obtained by our proposed method. Each pair of mutually connected subregions depicted in the same color belongs to the same cluster. L and R denote the left and right hemispheres, respectively

somatosensory zone, and posterior parietal/occipital zone, as prior brain targets (Figure 6a) (Zhang et al., 2008, 2010). By contrast, cortical regions automatically identified through our method are well-studied brain networks, which are frontoparietal network, default mode network, visual network, sensorimotor network, and precuneus network (Figure 3). Therefore, the thalamic subregions co-partitioned by our method, respectively connecting with one of the simultaneously identified well-studied brain networks, are more meaningful and interpretable than the prior connectivity based mapping method.

In addition, the proposed method is a data-driven approach, which could construct inherent connectional topography of the human brain. While the ICA based mapping method is a data-driven approach as well (O'Muircheartaigh et al., 2011; O'muircheartaigh et al., 2015; O'muircheartaigh & Jbabdi, 2018, 2015; Wu et al., 2018; Yuan et al., 2016). The ICA based mapping method usually identifies mutually connected subclusters between two brain ROIs based on their connectivity matrix (Wu et al., 2018). However, the cortical

clusters obtained by the ICA based mapping method are dispersely distributed anatomical regions rather than well-studied brain networks, which could be identified through the proposed method as shown in Figures 3 and 6b. Besides the ICA based mapping method, the normalized cut based mapping method is also a data-driven approach selected for comparison. As shown in Figure 6c, the normalized cut based mapping method is capable of identifying well-studied brain networks, such as default mode network, visual network, and sensorimotor network. Nevertheless, the largest subregion of the thalamus was identified solely from the thalamocortical system, whose mutually connected cortical subregion was not extracted by the normalized cut based mapping method.

Quantitatively, the proposed method achieved the highest functional homogeneity gauged by modified SI value among existing methods, which is gauged by SI with the larger value indicating higher functional homogeneity of the mapped connectional topography (Cheng et al., 2014, 2020; Craddock et al., 2012). As listed in Table 1, SI values of the constructed connectional topography by our method
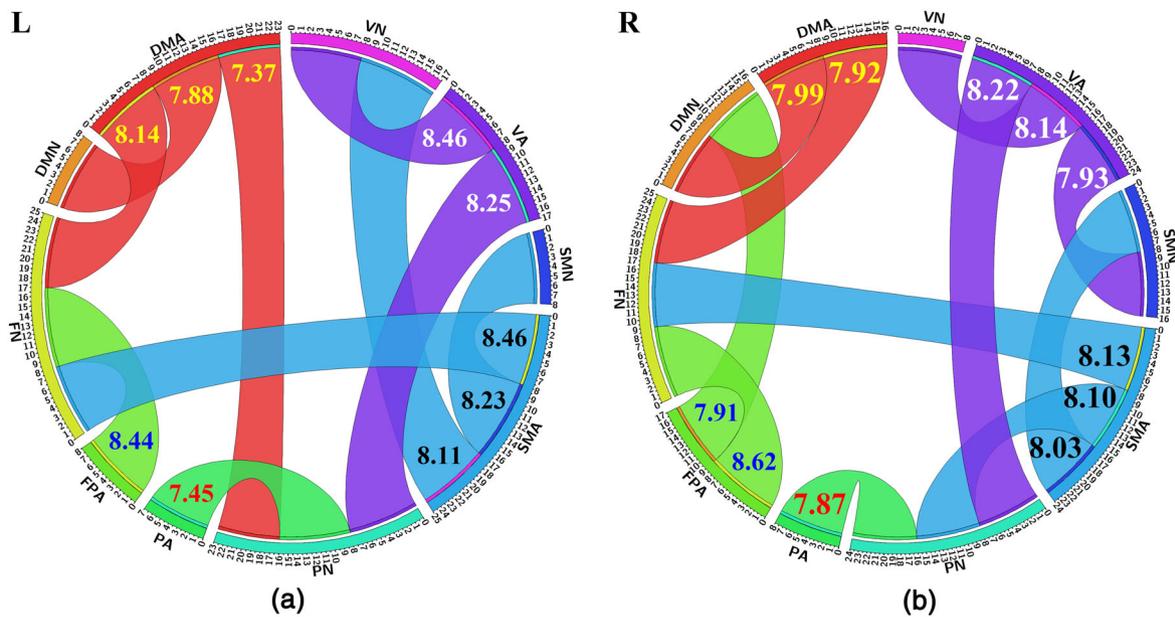
FIGURE 4 Functional interconnections between thalamic subregions and cortical subregions from the mapped thalamocortical connectional topography at group level. (a) and (b) top-3 significant functional connections between each thalamic subregion and each cortical subregion graphically rendered as a connectogram for left and right hemispheres, respectively. In panels (a, b), group-level functional connection strengths (z values) represented by the opacity of the line are displayed as edges. The subregions, including FPN, DMN, VN, SMN, and PN, are identified cortical networks by our proposed co-clustering based method, while FPA, DMA, VA, SMA, and PA are corresponding co-partitioned thalamic subregions. Abbreviations: FPN, frontoparietal network; DMN, default mode network; VN, visual network; SMN, sensorimotor network; PN, precuneus network; FPA, frontoparietal area; DMA, default mode area; VA, visual area; SMA, sensorimotor area; PA, precuneus area; L, left hemisphere; R, right hemisphere
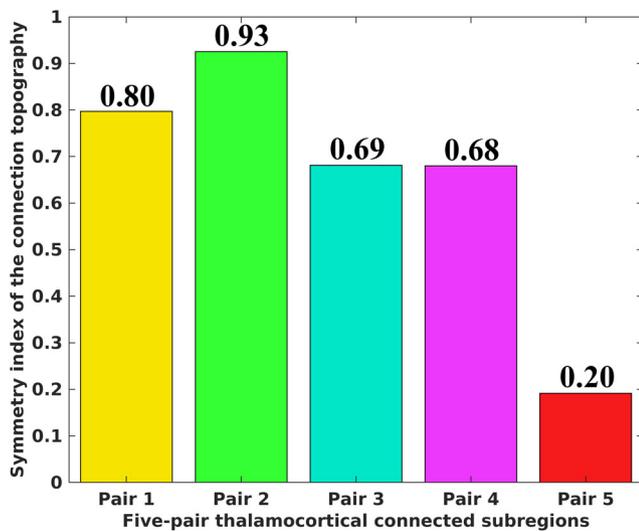
FIGURE 5 Symmetry of the mapped connectional topographies of bilateral thalamocortical systems between two hemispheres. Pairs 1–5 represent frontoparietal area with frontoparietal network, default mode area with default mode network, visual area with visual network, sensorimotor area with sensorimotor network, and precuneus area with precuneus network, respectively

connectional topography mapping method is superior to the existing methods.

4 | DISCUSSION

In this study, we proposed a novel co-clustering based method for mapping the inherent connectional topography of the human brain based on rs-fMRI data. We addressed two major challenges in connectional topography construction as follows. Firstly, the number of clusters was automatically determined based on clustering quality. Moreover, the proposed method is a data-driven approach for mapping connectional topography. Thus, this method could construct more meaningful, interpretable, and homogeneous connectional topography compared with the existing hypothesis-driven method and two other data-driven methods (Van Den Heuvel et al., 2008; Wu et al., 2018; Zhang et al., 2008, 2010), and the mapped connectional topography with the proposed method was quite symmetrical between two hemispheres as well.

4.1 | Determination of optimal clustering number

The decision upon the optimal number of clusters for mapping connectional topography remains a major challenge. An objective criterion (i.e., modified SI index measuring clustering quality) is accurate in

are higher than the prior connectivity, the ICA and the normalized cut based mapping methods. These qualitative and quantitative comparisons have demonstrated that the proposed co-clustering based
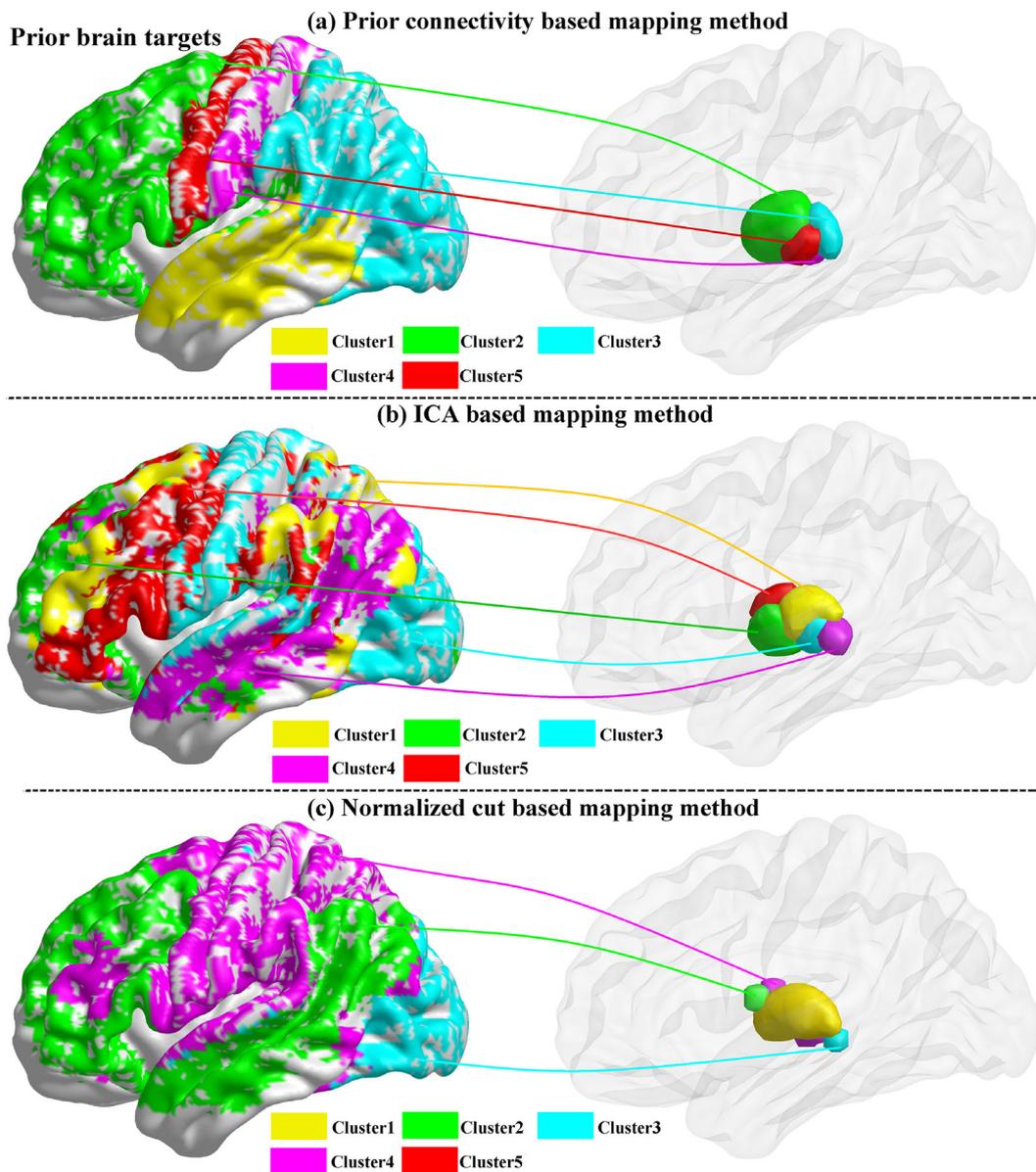
FIGURE 6 Mapped thalamocortical connectional topography with existing methods, including prior connectivity based mapping method, ICA based mapping method, and normalized cut based mapping method. Abbreviation: ICA, independent component analysis

identifying the correct number of functional clusters in combination with appropriate brain parcellation method reported in a previous fMRI study (Ryali, Chen, Padmanabhan, Cai, & Menon, 2015). This is to say that the modified SI index could accurately uncover the optimal number of clusters from rs-fMRI data for parcellating the brain. In the present study, the objective criterion (namely modified SI index) was chosen for determining the optimal number of clusters in combination with the proposed co-clustering based connectional topography mapping method. The optimal clustering number $k^* = 5$ was successfully identified for mapping thalamocortical connectional topography based on rs-fMRI data using the modified SI index, that is, the mapped five-cluster thalamocortical connectional topography was the optimal solution with the global maximum SI value among $k = 2, 3, …,$ and K cluster solutions for both left and right hemispheres, respectively. The

parameter K was set to 10 due to relatively low spatial resolution of the rs-fMRI data. The modified SI index as the objective criterion combined with the proposed method might be a desirable strategy for uncovering the correct number of clusters from data in brain connectional topography mapping.

4.2 | Proposed method versus existing mapping methods

The proposed novel co-clustering based mapping method is a different approach to automatically construct the connectional topography of the human brain compared with existing mapping methods. The proposed method could construct inherent connectional topography

TABLE 1 Quantitative comparison of existing methods and ours through connectional topography mapping of bilateral thalamocortical systems with respect to functional homogeneity measured by modified silhouette width (SI) index

Methods	SI (left hemisphere)	SI (right hemisphere)
Our method	**0.33**	**0.34**
ICA based method	0.28	0.30
Prior connectivity based method	0.20	0.26
Normalized cut based method	0.09	0.19

Note: The existing methods are the ICA, prior connectivity and normalized cut based methods. The bold values for the SI index represent the largest value among existing methods and ours, and the larger SI value denotes higher functional homogeneity for mapped connectional topography. Abbreviation: ICA, independent component analysis.

in a data-driven manner, which was validated by mapping the thalamocortical connectional topography as shown in Figure 3. The proposed method not only parcellates the substructure (i.e., thalamus here), but also identifies their respective connected cortical networks. Therefore, the proposed method is an effective data-driven approach for mapping the inherent connectional topography of the human brain. For existing methods, the prior connectivity based mapping method requires prior defined brain targets (Figure 6a), the ICA based mapping method is not robust enough (Figure 6b), and the normalized cut based mapping method is not sufficiently suitable for constructing the connectional topography between two brain ROIs of a certain neural circuit under consideration (Figure 6c). Therefore, the mapped connectional topography with the existing methods might deviate from data as compared with the proposed method as shown in Figures 3 and 6.

Furthermore, the proposed method outperformed existing methods with respect to functional homogeneity of the mapped connectional topography (Table 1), which further confirms that our proposed method is more faithful to data than existing methods. Overall, the proposed novel, data-driven method could construct inherent connectional topography of the human brain by leveraging the power of the co-clustering.

4.3 | Interpretability of the mapped connectional topography

The mapped connectional topography with the proposed method is neurobiologically interpretable, which was validated through connectional topography mapping of the thalamocortical system (Figure 3). Particularly, the identified cortical networks are well-studied brain functional networks, including frontoparietal network, default mode network, visual network, sensorimotor network, and precuneus network. These identified cortical networks are neurobiologically

meaningful. Therefore, the co-partitioned thalamic subregions are neurobiologically meaningful as well, which can be indirectly verified through their mutually connected these brain functional networks. Although the precise functional roles that the co-partitioned thalamic subregions play with regard to their mutually connected brain functional networks are uncertain, the present study reinforces the evidence of the presence of diverse functional interactions between thalamus and cortex at a fine granularity. In addition, the pair-wisely connected subregions of the mapped connectional topography between two hemispheres have high symmetry ranging from 0.20 to 0.93 (Figure 5), which provides sufficient face interpretability for mapped connectional topography. Overall, the mapped connectional topography with the proposed method has good interpretability.

4.4 | Limitations and future work

There are several limitations in the present study. Firstly, the connectional topography was constructed at the group level, which might misrepresent the underlying individual connectional organization due to inter-individual variability. The poor SNR of fMRI data is needed to be improved for mapping connectional topography of the brain at the individual level in future work. In addition, the granularity of the mapped connectional topography was not fine enough, which was limited by the relatively low spatial resolution of the rs-fMRI data. More work should focus on mapping fine granularity connectional topography of the brain using fMRI data with high spatial resolution. Furthermore, the proposed connectional topography mapping method could not extract mutually functionally anticorrelated subregions, and could not estimate the functional connectivity strength of the extracted mutually connected subregions as well. Usually, post hoc processing is needed to compute the functional connectivity of the resulting subregions identified by the proposed method. So, the functional connectivity obtained by the post hoc processing might be inconsistent with the connectional topography mapped by the proposed method. Further work needs to be undertaken to address these drawbacks of the proposed method for better revealing the connectional organization of the human brain.

5 | CONCLUSIONS

In this study, we have proposed a novel, fully data-driven, co-clustering based method for mapping inherent functional connectivity topography of the human brain. The optimal clustering number in the proposed method was automatically determined based on clustering quality. The validation results have demonstrated that the proposed method could construct neurobiologically meaningful and homogeneous connectional topography, which outperforms existing connectional topography mapping methods. The validity of the proposed method was further strengthened by the high symmetry of the mapped connectional topography between two hemispheres. The proposed method provides a new perspective to unveil the

topographic organization of the human brain, which might facilitate a better understanding of the brain connectional organization under normal and disease states. In the future, the proposed method will be further validated through constructing connectional topography of other neural circuits based on functional or structural connectivity information.

CONFLICT OF INTERESTS

The authors declare no competing interest.

DATA AVAILABILITY STATEMENT

Data were provided [in part] by the Consortium for Reliability and Reproducibility (Consortium Founders: Xi-Nian Zuo and Michael P. Milham) contributed by Principal Investigator Yong He.

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