RESEARCH ARTICLE

The fronto-insular cortex causally mediates the default-mode and central-executive networks to contribute to individual cognitive performance in healthy elderly

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Abstract

The triple network model that consists of the default-mode network (DMN), central-executive network (CEN), and salience network (SN) has been suggested as a powerful paradigm for investigation of network mechanisms underlying various cognitive functions and brain disorders. A crucial hypothesis in this model is that the fronto-insular cortex (FIC) in the SN plays centrally in mediating interactions between the networks. Using a machine learning approach based on independent component analysis and Bayesian network (BN), this study characterizes the directed connectivity architecture of the triple network and examines the role of FIC in connectivity of the model. Data-driven exploration shows that the FIC initiates influential connections to all other regions to globally control the functional dynamics of the triple network. Moreover, stronger BN connectivity between the FIC and regions of the DMN and the CEN, as well as the increased outflow connections from the FIC are found to predict individual performance in memory and executive tasks. In addition, the posterior cingulate cortex in the DMN was also confirmed as an inflow hub that integrates information converging from other areas. Collectively, the results highlight the central role of FIC in mediating the activity of large-scale networks, which is crucial for individual cognitive function.

KEYWORDS

Bayesian network, directed connectivity, fronto-insular cortex, posterior cingulate cortex, salience network, triple network model

1 | INTRODUCTION

Unveiling the secret of human mind relies ultimately on the knowledge of the working principles of our heavily connected brain (Turk-Browne, 2013). It is of fundamental importance to characterize the organizational architecture of the brain for understanding the transfer and processing of neuronal information across the distribution of interconnected brain regions (Power et al., 2011; Yeo et al., 2011).

Functional magnetic resonance imaging (fMRI), which measures the blood-oxygen-level dependent (BOLD) signals, has rapidly gained popularity for investigation of the large-scale network dynamics over widely distributed brain regions (Bressler & Menon, 2010; Li et al., 2011; Park & Friston, 2013; Turk-Browne, 2013). The distributed regions that are coactivated during tasks have been found to be shaped by intrinsic networks, which are active during the resting state (Cole, Bassett, Power, Braver, & Petersen, 2014; Smith et al., 2009;

Tavor et al., 2016) and are closely related to individual behavior and cognition (Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015; Schultz & Cole, 2016; Zou et al., 2013).

Of the large-scale intrinsic networks in the human brain, the default-mode network (DMN), central-executive network (CEN), and the salience network (SN), which are collectively referred to as the triple network model, are the most crucial networks that are extensively involved in diverse cognitive and emotional processes (Greicius, Krasnow, Reiss, & Menon, 2003; Menon, 2011; Seeley et al., 2007). The DMN is a medial-fronto-medial-parietal system anchored in the medial prefrontal cortex (MPFC) and the posterior cingulate cortex (PCC) (Greicius et al., 2003). It is typically deactivated during various attention-demanding tasks, and activated in self-referential mental processes (Greicius et al., 2003; Sheline et al., 2009; van Buuren, Gladwin, Zandbelt, Kahn, & Vink, 2010). The CEN is a fronto-parietal system anchored bilaterally in the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) (Seeley et al., 2007). It is largely involved in higher cognitive functions including working memory, attentional control, decision-making, and problem-solving (Koechlin & Summerfield, 2007; Volk & Lewis, 2010). The SN is a cingulo-opercular system anchored in the fronto-insular cortex (FIC) and the anterior cingulate cortex (ACC) (Menon, 2011). It is crucially involved in the detection, filtration, and orientation of relevant information received from external stimuli or internal events (Menon, 2011; Seeley et al., 2007; Uddin, 2015).

A central hypothesis regarding the triple network model is that the SN, particularly the FIC, acts as an integral hub that causally mediates dynamic interactions between the DMN and the CEN (Menon, 2011; Menon & Uddin, 2010; Uddin, 2015; Uddin, Kinnison, Pessoa, & Anderson, 2014). The FIC is involved in salience processing across multiple sensory, emotional, and cognitive domains (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Uddin, 2015). Salience signals induced by internally oriented mental thoughts originating in the DMN or externally oriented attention mediated by the CEN are suggested to be mapped into the FIC in the SN (Menon, 2011). Disrupted connectivity of the FIC prevents it from exerting effective transient control on other networks, leading to mental or cognitive deficits in mental illnesses, such as depression (Hamilton et al., 2012; Wiebking et al., 2010) and dementia (Day et al., 2013). Another noteworthy region is the PCC from the DMN, which has been consistently documented as a causal inflow hub that integrates information from the whole brain (Buckner et al., 2009; Dai et al., 2015; Fransson & Marrelec, 2008; Li et al., 2011). In the framework of the triple network model, several recent studies have investigated the functional interactions between these networks via intervention techniques or computational methods. Chen et al. (2013) demonstrated a causal influence of CEN and SN on the DMN, using transcranial magnetic stimulation (TMS) (Chen et al., 2013). Cao et al. (2016) observed increased and sustained anti-correlation of DMN with CEN and SN after 3 months of cognitive training in healthy elderly individuals (Cao et al., 2016). Using Granger causality analysis, Uddin, Supekar, Ryali, and Menon (2011) found increased causal influence of the FIC on CEN in adults, compared to children (Uddin et al., 2011). Ryali et al. (2016) further characterized the temporal switching between the triple networks associated with maturation, using a variational Bayesian Hidden Markov Model (Ryali

et al., 2016). Liang, Zou, He, and Yang (2016) observed that the connectivity of both CEN and DMN with SN is strengthened with increasing load of working memory task, using a graph-based modularity analysis (Liang et al., 2016). Although these studies have examined the connectivity relationships between diverse regions in the triple network, the hypothesis of FIC acting as a causal outflow hub that mediates the activity of the triple network requires further confirmation. In view of previous studies on the DMN and PCC, it is also interesting to examine whether the PCC acts as a causal inflow hub that integrates information within the framework of the triple network model.

In this study, to test the hypothesis regarding the roles of the FIC and PCC in the triple network model, a combination of group-independent component analysis (ICA) and Bayesian network (BN) learning approach was applied on an exploratory resting-state fMRI data set collected from 88 healthy elderly individuals and a validation data set collected from 45 healthy older adults. We employed Group ICA to isolate the DMN, CEN, and SN (Greicius, Srivastava, Reiss, & Menon, 2004; Li et al., 2012; Seeley et al., 2007) from the resting-state data. BN is a machine learning approach that can estimate the causal relationships by searching the conditional dependencies and independencies between variables in a data-driven and global-learning manner. In our previous studies, we have used the BN to characterize the network-level whole-brain connectivity (Li et al., 2011) and the DMN disruptions in Alzheimer's disease (Li et al., 2013; Wu et al., 2011). In the current study, we employed the BN to understand the architecture of directed connectivity between the regions and networks in the triple network model for elucidating the roles of FIC and PCC in connectivity. Moreover, as many studies have found the correlation between these three networks and individual cognition (Liang et al., 2016), we were particularly interested in examining the cognitive significance of the causal connectivity of FIC and PCC. Specifically, we evaluated the performance of participants in tasks assessing executive function and memory with standardized psychometric questionnaires. We examined whether a stronger mediating role for the FIC or a stronger integrating role for the PCC in the triple network model is associated with a better cognitive ability.

2 | MATERIALS AND METHODS

2.1 | Subjects

Eighty-eight cognitively normal older adults (70.2 ± 5.6 years; range: 60–80 years; 40 males and 48 females) were included in this exploratory analysis of the three functional networks. All participants met the following inclusion criteria: (a) a score ≥ 21 on the Beijing Version of the Montreal Cognitive Assessment (MoCA) (Yu, Li, & Huang, 2012); (b) a score ≤ 16 on the Activities of Daily Living (ADL) (Lawton & Brody, 1969); (c) the absence of neurological deficits and traumatic brain injury; (d) not exhibiting dementia or mild cognitive impairment; and (e) right-handed.

Brain imaging data of each subject was acquired under resting-state conditions using a 3.0 Tesla Siemens Trio scanner (Erlangen, Germany), located at the Beijing MRI Center for Brain Research.

T2*-weighted functional images were collected using an echo-planar image (EPI) sequence with the following parameters: time repetition (TR) = 2000 ms; time echo (TE) = 30 ms; flip angle = 90°; field of view (FOV) = 200 mm × 200 mm; thickness = 3.0 mm; gap = 0.6 mm; matrix = 64 × 64; in-plane resolution = 3.125 × 3.125; and 33 slice. Each functional scan consisted of 200 volumes and lasted for 6 min and 40 s. T1-weighted anatomical images were collected using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 1900 ms; TE = 2.2 ms; flip angle = 9°; matrix = 256 × 256; voxel size = 1 mm × 1 mm × 1 mm, and 176 slices.

Executive function was evaluated in a subset of 76 subjects (70.7 ± 5.5 years; range: 60–80 years; 35 males and 41 females), using the psychometric questionnaires of the digit span test (backward), category fluency test (food), and the trail making test (B-A). Memory was evaluated in a subset of 45 subjects (71.0 ± 5.9 years; range: 60–80 years; 15 males and 30 females), using the paired associative learning (PAL) test and the logical memory subset of Wechsler Adult Intelligence Scale (WAIS). The exploration data set column in Table 1 shows the demographical and neuropsychological information for included participants in the exploratory analysis.

The study was approved by the institutional review board of the Institute of Psychology, Chinese Academy of Sciences. All participants provided written informed consent before taking part in our experiments.

2.2 | Image preprocessing

The Statistical Parametric Mapping program (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) and the tool box for Data Processing & Analysis for Brain Imaging (DPABI; <http://rfmri.org/dpabi>) were used for imaging data preprocessing. This included the removal of the first five volumes, corrections for the intra-volume acquisition time differences using the Sinc interpolation, corrections for the inter-volume geometrical displacement using the spatial transformation of a six-parameter rigid body, normalization to the Montreal Neurological Institute (MNI) space (resampling size = 3 mm × 3 mm × 3 mm) using the DARTEL approach (Ashburner, 2007), and spatial smoothing with a 4-mm full width at a half maximum Gaussian kernel. Quality control (QC) was performed in DPABI using a five-point scoring method to visually inspect the quality of images for both the raw structural and functional images, as well as the coregistration accuracy. Each included participant had a QC score ≥ 3, and a head movement less than 2.0 mm translation and 2.0° rotation, during the scanning. The residual volumes were entered for the Group ICA analysis. In the BN connectivity analysis of regional time series, images were further preprocessed using the DPABI, including de-trending and temporal band-pass filtering (0.01–0.08 Hz) to reduce the effects of low-frequency drifts and high-frequency physiological noise, a nuisance regression of the head motion, using a Friston 24-parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) (Friston, Williams, Howard, Frackowiak, & Turner, 1996) with scrubbing (Power et al., 2014; Satterthwaite et al., 2013; Yan et al., 2013), and the regression of the white matter and cerebrospinal fluid signals, which were calculated by averaging the

TABLE 1 Demographical and neuropsychological characteristics of participants

Variables	Exploration data set (n = 88)	Validation data set (n = 49)
Sex (male/female)	40/48	12/37
Age (years)	70.2 ± 5.6	67.1 ± 4.8
Education (years)	13.9 ± 3.5	12.2 ± 2.8
MoCA-Beijing	26.7 ± 2.3	28.1 ± 1.7
Activities of daily living	14.0 ± 0	–
Digit span (backward)	4.7 ± 1.5 ^a	5.1 ± 1.2
Trail making A (s)	41.7 ± 20.8 ^a	36.8 ± 11.8
Trail making B (s)	75.4 ± 39.3 ^a	76.3 ± 29.5
Category fluency (food)	23.9 ± 6.6 ^a	24.7 ± 5.7
Paired associative learning	13.4 ± 4.3 ^b	10.8 ± 3.7
WAIS (logical)	9.2 ± 2.8 ^b	–

Note: Mean ± SD for scores on demographical and neuropsychological assessments.

^a Information available from 76 participants.

^b Information available from 45 participants.

voxel signals within the SPM a priori masks (white.nii and csf.nii, respectively), thresholded at 99%.

2.3 | Group ICA of the triple networks

Group ICA was used to separate the triple networks including the DMN, CEN, and SN from the preprocessed data. The Group ICA was performed using the group ICA of fMRI Toolbox (GIFT; <http://icatb.sourceforge.net>), and included two rounds of principal component analysis (PCA) for reduction of fMRI data dimension, separation of the independent components (ICs) from the group-aggregated data, and back reconstruction of individual-level ICs. The Infomax algorithm (Lee, Girolami, & Sejnowski, 1999) was employed to split the data sets into a set of 24 ICs based on the minimum description length (MDL) criteria. PCA was first applied to each subject to reduce the preprocessed data into 36 principle components, which were then appended along the time dimension and further reduced to 24 principle components via another PCA. Robust estimation of the ICs was achieved by running the ICA 100 times using the ICASSO algorithm (Himberg, Hyvarinen, & Esposito, 2004) implemented in GIFT. Three ICs were manually selected for representing triple networks with reference to previously reported network patterns (Menon, 2011). To improve the normality of intensity (functional connectivity) values of voxels in each IC, z-score scaling was applied to the spatial components of each subject, normalizing them to zero mean and unit variance. Finally, to derive the group functional connectivity of the DMN, CEN, and SN, voxel-wise one sample *t* tests (corrected *p* < .001 by false discovery rate [FDR], cluster size >100 voxels) were performed with these individual components.

2.4 | BN analysis of the triple network model

The BN was used to model the directed functional interactions in the triple network model. The nodes in the BN were defined as the regions from the three networks. Combining the ICA-defined network

patterns and referring to previous literature, we selected nine regions of interest (ROIs) including the MPFC and PCC from the DMN, the bilateral DLPFC and bilateral PPC from the CEN, and the ACC and the bilateral FIC as nodes in the BN model. Each ROI was defined as a sphere (radius = 6 mm) centered on the voxel with the highest significance of the component map. Time series of each ROI was calculated as the average of the time courses of all voxels within the spherical ROI. Gaussian BN conditional dependence relationships learning between the time series of these nine ROIs was guided by a Bayesian information criterion (BIC)-based "search + score" approach. The model that best fit the BIC was identified as an optimal estimation of the BN interactions in the triple network model. In addition, we also explored the network level BN interactions between the triple networks by averaging time series of ROIs from the same functional network. The BN structure and parameters were learned using the sparsity-promoting L1-regularization paths algorithm (Schmidt, Niculescu-Mizil, & Murphy, 2007) and the maximum likelihood estimation algorithm, respectively, that were implemented in the MATLAB BN toolbox (<https://code.google.com/p/bnt/>). Detailed descriptions of the BN methodology could be found in our previous publications, where we have successfully used these BN algorithms to characterize the directed connectivity of large-scale resting-state networks and the connectivity disruptions of the DMN in Alzheimer's disease (Li et al., 2011; Li et al., 2013; Wu et al., 2011).

The BN connectivity roles of the nine regions in the triple network model were differentiated in terms of the number of in-going and out-going connections. The region with maximal number of out-going connections was speculated to be the causal outflow hub, while the region with maximal number of in-going connections was speculated to be the causal inflow hub. This index was facilitated to test the hypothesis regarding the outflow hub for FIC and the inflow hub for PCC in the triple network model.

2.5 | Connectivity-cognition correlations

To explore the cognitive significance of the BN connectivity of the triple network model, we examined whether the BN connectivity variables relate to cognitive abilities of these older adults. We were particularly interested in examining whether a stronger mediating role for the FIC or integrating role for the PCC is associated with better cognitive performance. We used the BN connectivity weights and the number of in-going/out-going connections to be represented as the connectivity variables. Cognitive variables include a memory composite and an executive composite. To calculate composite scores, raw test scores for each participant were converted to z-scores using the mean and SD for each test, and the z-scores of the tests composing each composite were averaged for each participant. The memory composite combined test scores from the PAL test and the logical memory subset of WAIS. The executive composite included the digit span test (backward), category fluency test (food), and the trail making test (B-A).

Pearson correlation for normally distributed data and Spearman rank correlation for nonparametric data were performed to test the cognitive significance of the BN connectivity at a threshold of one-tailed $p < .05$ (Bonferroni corrected). Normality of data was examined

using the Kolmogorov-Smirnov test, and $p > .05$ indicated no significant deviation from normality.

2.6 | Validation analysis

We applied the nine ROIs as defined above to an independent replication of resting-state fMRI data set ($N = 49$; 12 males and 37 females; 67.1 ± 4.8 years of age), to further validate the BN-based triple network model connectivity. This validation data set was collected using a Philips Achieva 3.0 Tesla MRI scanner (Philips Healthcare, Andover, MA) at the MRI Center of the First Hospital of Hebei Medical University of China. T2*-weighted functional images were collected using an EPI sequence with TR = 2,000 ms, TE = 30 ms, flip angle = 90° , FOV = 200 mm $\times$ 200 mm, thickness = 3.6 mm, matrix = 112×112 ; in-plane resolution = 1.786×1.786 , 33 axial slices, and 200 volumes. Each functional scan also lasted for 6 min and 40 s. T1-weighted MPRAGE image was collected with the following parameters: TR = 1,900 ms; TE = 2.2 ms; matrix = 256×256 ; voxel size = $1 \times 1 \times 1$ mm³; flip angle = 9° , and 176 slices. The validation data set column in Table 1 shows the demographical and neuropsychological information for included participants in the replication analysis.

Global signal regression is a controversial step in the preprocessing that may significantly influence the result of connectivity. Previous studies showed that the regression of global signals may introduce undesirable negative connectivity that are otherwise largely absent (Fox, Zhang, Snyder, & Raichle, 2009; Gotts et al., 2013; Saad et al., 2013), but recent studies suggest that the global signal regression can further decrease dependence on motion and remove artifactual variance (Power et al., 2014; Satterthwaite et al., 2013; Yan et al., 2013). In view of these debates, we finally reconstructed the BN connectivity model for the two data sets with global signal further removed.

3 | RESULTS

3.1 | Directed architecture of the triple network model

We first used Group ICA to separate the triple networks from the resting-state data. Figure 1 shows the functional connectivity patterns of the DMN (component IC7), CEN (component IC10), and SN (component IC13) in the triple network model (corrected by FDR with $p < .001$; cluster size >100 voxels). Spatial maps of all 24 components derived from Group ICA were demonstrated in Supporting Information Figure S1. To create regions for BN analysis, we defined nine regions (peak coordinates are in the space of MNI) based on the ICA-based result, including the MPFC ($-3, 54, 15$) and PCC ($-3, -54, 30$) in the DMN, the bilateral DLPFC (L: $-42, 51, 6$; R: $27, 18, 54$) and bilateral PPC (L: $-39, -63, 48$; R: $51, -54, 42$) in the CEN, and the bilateral FIC (L: $-39, 0, 12$; R: $39, 6, 6$) and ACC ($0, 21, 30$) in the SN. We note here that the component IC7 was selected as the DMN as it better coincided with the typical DMN pattern that included the MPFC, PCC, and bilateral parietal cortices. Whereas the component IC17 (Supporting Information Figure S1) only covered the posterior DMN, and did not include the anterior MPFC that was used for following BN

FIGURE 1 The DMN, CEN, and SN in the triple network model estimated by group ICA (one sample *t* test, FDR corrected $p < .001$, cluster size > 100 voxels). *T* value bars are shown on the right [Color figure can be viewed at wileyonlinelibrary.com]

analysis, thus we selected IC7 that included both the MPFC and the PCC to define the two crucial regions in the DMN.

The directed interactions between the triple networks were learned using the BN (Figure 2a). At a network level, the result shows a direct outflow from the SN to the DMN and CEN ($SN \rightarrow DMN/CEN$), and the DMN receives activity inflow from the SN and CEN ($SN/CEN \rightarrow DMN$). Regional BN analysis demonstrates that the bilateral FIC in the SN acts as a node that does not receive flow of in-going activity but only generates a flow of out-going activity to regions in other networks. Specifically, the rFIC directly influences the activity of the bilateral DLPFC, bilateral PPC, and the PCC; the lFIC directly influences the activity of the lDLPFC, lPPC, and MPFC, and indirectly influences the rDLPFC, rPPC, and PCC via the rFIC. The PCC acts as an opposite node that does not generate out-going connections but only receives in-going connections from all other regions of the triple network. We also calculated the number of in-going and out-going connections associated with each of the nine ROIs in the model. As shown in Figure 2b, the bilateral FIC ranks first in the proportion of the number of outflow connections, followed by the bilateral DLPFC, ACC, bilateral PPC, MPFC, and the PCC. Similarly, the PCC takes the first place in the proportion of the number of inflow connections.

3.2 | Cognitive significance of the triple network interactions

To examine whether a stronger mediating role for the FIC or integrating role for the PCC in the triple network model is associated with better cognitive performance, we correlated composite scores of individual memory and executive function to the connectivity strength of the connections associated with FIC or PCC, and to the number of out-going connections of the FIC, and the number of in-going connections of the PCC. For the examination of correlations between

FIC/PCC connection numbers and cognitive performance in memory and executive functions (Bonferroni-corrected α threshold of $0.05/4 = 0.0125$), the result, as shown in Figure 3, revealed that larger number of outflow connections in the FIC were significantly associated with better performance in both executive (Spearman's $\rho = .284$, $p = .007$) and memory functions (Spearman's $\rho = .358$, $p = .009$). The PCC outflow number was not correlated with either of the two cognitive composites. No correlation between FIC/PCC connectivity strength and cognitive performance reached a Bonferroni-corrected α threshold of $0.05/18 = 0.0028$. With more liberal uncorrected $p = .05$, we observed a trend that stronger

FIGURE 2 The BN connectivity of the triple network model. (a) Directed connectivity of the triple network model learned by group BN with aggregate data from all subjects. Connections initiated from the SN, CEN, and DMN are shown in red, green, and blue, respectively, where the darker shades denote inter-network connections and lighter shades denote intra-network connections. The dashed connectivity denotes network-level BN connectivity, which is learned by averaging the time courses of the selected ROIs within each network. Line width is proportional to the weight of connectivity weight coefficient. (b) the bar graphs show the order of the mean proportion of in-going and out-going connections for the nine ROIs from the triple networks. The proportion of the in-going/out-going connections was calculated as the number of in-going/out-going connections divided by the total number of connections associated with each ROI for each subject. The histogram shows the mean proportion of in-going/out-going connections across all subjects. Error bars refer to standard error [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Correlation between the number of out-going connections of the FIC and cognitive performance. The total number of out-going connections from bilateral FIC is significantly correlated with (a) executive and (b) memory test scores. Each dot denotes one participant. Age and gender were controlled

connectivity weights from the IFIC to the IDLPFC ($IFIC \rightarrow IDLPFC$), and from the rFIC to the PCC ($rFIC \rightarrow PCC$) were correlated with better executive function (Pearson's $r = .242$, $p = .019$ and Pearson's $r = .223$, $p = .028$, respectively; Figure 4).

3.3 | Validation of the BN-based triple network model

A BN analysis of the triple network model in an independent validation data set robustly repeated the result (Figure 5a). Comparing the BN interactions of the triple networks in two different data sets, the result consistently demonstrates that the SN causally influences activity of the DMN and CEN, while the DMN receives information flow from the DMN and CEN. In the regional BN interactions, the bilateral FIC reliably acts as a causal outflow hub that does not receive in-going connections but conformably generates out-going connections to regions in other networks, and conversely the PCC acts as an inflow hub that does not generate out-going connections but only receives in-going connections from all other regions in the triple networks. The outflow connections from the bilateral FIC and the inflow connections to the PCC as observed in Figure 2a, were all robustly repeated in this

independent validation data set. We also validated the cognitive significance of the BN connectivity variables including the number of FIC causal outflows and the connectivity weights of $IFIC \rightarrow IDLPFC$ and $rFIC \rightarrow PCC$. At a Bonferroni-corrected α threshold of 0.008 (0.05/6), the above significant correlation was partly replicated as stronger causal connectivity from rFIC to PCC correlated with better memory (PAL test) performance in this validation data set (Pearson's $r = .395$, $p = .003$; Figure 5b).

To exclude the possibility of the influence of global signal on BN-based triple network interactions, we reanalyzed the regional BN connectivity using the data with global signal removed in the two data sets. As shown in Supporting Information Figure S2, the global signal regression does not influence the network level interactions of the triple network model in both the exploration data set and the validation data set. In the regional level of exploratory data set, although there are three more outflow connections ($rFIC \rightarrow MPFC$, $IFIC \rightarrow rDLPFC/PCC$) emerging from the bilateral FIC, all other connections with IFIC and rFIC were repeated in the data with global signal removed, and there is no connection flowing from regions in other two networks to the bilateral FIC. Similarly, the PCC consistently acts as an inflow hub that does not generate connections but only receives connections

FIGURE 4 Correlation between FIC connectivity and cognitive performance. The directed connectivity from the IFIC to IDLPFC in the CEN (a) and rFIC to PCC in the DMN (b) show correlation trends with the score in the executive composite. Each dot denotes one participant. Age and gender were controlled

FIGURE 5 Reproducibility analysis in the validation data set. (a) the BN connectivity of the triple network model learned from the validation data set. (b) the correlation between BN connectivity weight from rFIC to PCC and memory (PAL test) performance in this data set [Color figure can be viewed at wileyonlinelibrary.com]

from all other regions directly or indirectly. In the validation data set, the bilateral FIC and PCC show identical directed connectivity patterns when using different approaches to preprocess global signal.

4 | DISCUSSION

In this study, we used a machine learning approach combined with Group ICA and BN to analyze the architecture of directed connectivity of the triple network model that consists of three core neurocognitive networks including the DMN, CEN, and SN. Data-driven exploration of regional connectivity relationships demonstrated two special hubs: a causal outflow hub executed by the FIC in the SN that exerts direct or indirect out-going connections to all other regions, and a causal inflow hub acted by the PCC in the DMN that aggregates global information through directed connections starting from all other regions. The replication of the exploratory finding on an independent sample further demonstrated the robustness of the results obtained for connectivity roles of the FIC and PCC in the triple network model by the BN learning approach. Moreover, we found that a stronger directed connectivity from the FIC to regions in the DMN and CEN is correlated with better performance, and the mediatory influence of the FIC on other regions is critically related to both memory and executive performance.

A major advantage of BN over traditional well-known directed connectivity methods, such as structural equation modeling (McIntosh & Gonzalez-Lima, 1994) and dynamic causal modeling (Friston, Harrison, & Penny, 2003), is that it learns networks from data, rather than examines a priori connectivity model for neural systems. A good agreement between the computational connectivity evidence from data-driven learning and previous cognitive evidences from experimental tasks could, therefore, better validate the triple network connectivity pattern. Another strength is that BN is able to capture a complex system in a complete global scale, which is superior to other pairwise learning approach, such as Granger causality analysis (Goebel, Roebroeck, Kim, & Formisano, 2003). Thus, the data-driven

and global mapping characteristics of BN ensure it as an ideal approach to find the triple network organization.

Analyzing network dynamics with ICA and BN, we have shown that while the spontaneous activity differentiates into functionally specific brain networks, it engages organized large-scale communication between these networks. It suggests the coexistence of separation and cooperation of information processing in the brain (Li et al., 2011; Power et al., 2011; Tononi, Sporns, & Edelman, 1994). A crucial clue to untangle the intricate functional interactions is to identify the topologically connected cores that may attract and disseminate the global communication (Sporns, 2013). Previously, whole-brain regional connectivity studies have demonstrated that the PCC and the FIC are two important members of cortical rich club (Harriger, van den Heuvel, & Sporns, 2012; Sporns, 2013). In this study, the FIC and the PCC are further confirmed as two special connectivity hubs that respectively ensure the divergence and convergence of information in the default-mode, central-executive, and salience networks. It is the first result obtained through a data-driven and unbiased globally directed connectivity learning algorithm to validate the hypothesis regarding the regional roles, particularly the causally outflow hub of the FIC in the model. Within the framework of BN, the functional activity in almost all regions is directly dependent on that in the FIC, suggesting its central influence over the regions in the triple networks. This is consistent with recent functional task imaging studies that have explicitly demonstrated the causal control of the FIC to the DMN and CEN in decision-making (Chand & Dhamala, 2016), working memory (Liang et al., 2016), and visual attention task (Sridharan, Levitin, & Menon, 2008). The unique position of the FIC demonstrated through computational deduction is supported by its particularity in anatomical connections (Uddin, 2015). Early animal studies have revealed that the FIC is structurally connected with multiple regions: sensory cortex, motor cortex, olfactory cortex, amygdala, orbitofrontal cortex, ACC, and most association areas in the brain (Mesulam & Mufson, 1982; Mufson & Mesulam, 1982). Probabilistic tractography studies in humans have also found that the FIC is extensively connected with the orbitofrontal cortex, inferior frontal cortex, anterior, and middle

temporal cortex (Cloutman, Binney, Drakesmith, Parker, & Ralph, 2012). In particular, the FIC and ACC in the SN exclusively contain unique spindle cells, called the von Economo neurons (VENs) (Evrard, Forro, & Logothetis, 2012; Watson, Jones, & Allman, 2006). The VENs are dendritic and thus proposed to be morphologically advantageous to relay the output neural signals from the FIC to other regions in the brain to facilitate the rapid execution of decisions in complex situations (Allman, Watson, Tetreault, & Hakeem, 2005). In a postmortem study of SuperAgers who have unusually high performance on memory, the VENs density in the SN regions was found much higher in SuperAgers than in comparison groups (Rogalski et al., 2013). We therefore speculate that the VENs and the extensive brain-wide anatomical connections constitute the physiological basis for the outflow of influential connections of the FIC on all other regions in the DMN and CEN. Taken together, the BN-based computational model suggests that the FIC in the SN acts uniquely as an outflow core that initiates causal control signals in the triple large-scale networks.

More interestingly, we found that the mediatory role of the FIC in the triple network during the resting-state significantly predicts individual task performance. Stronger influence of the FIC on the triple networks, as indexed by the number of outflow connections and the weight coefficient of directed connectivity, correlated with better performance in both memory and executive tasks. Previous studies have demonstrated that the connectivity of each of the triple networks is closely related to individual cognition (Bressler & Menon, 2010). The present study expands on these findings to suggest the cognitive significance of the FIC as the causal outflow hub in the triple neurocognitive network model. To the best of our knowledge, this is the first study to explicitly report the correlation between FIC directed connectivity and cognitive function via computational learning. In addition, the index of outflow degree reveals that the FIC initiates more directed connections to achieve better cognitive performance. The more directed connections may computationally suggest more efficient divergence of information from the FIC to regions in the triple networks. Previous studies on resting activity and task activation have shown that the resting-state networks reflect the paths by which activity flows in the process of performing tasks (Cole et al., 2014; Cole, Ito, Bassett, & Schultz, 2016). Stronger FIC influential control connections preconfigured during the resting-state could be more efficiently invoked during executive tasks (Schultz & Cole, 2016), and therefore, explains its positive correlation with performance as observed while the psychometric tests in the present study were performed.

There are several issues that should be addressed in future studies. First, although the participants in the present study are older adults with normal cognition, we did not intend to investigate the effect of aging on the triple network connectivity, or conclude that the finding in the present study is specific to the older-adult population. The focus here is to use two independent resting-state fMRI data sets from older adults to examine and validate the hypothesis regarding the mediating role of the FIC inherent in the triple network model. It would be interesting in future studies to apply the present method to other populations including young adults to further examine this hypothesis or to investigate the effect of aging on the FIC connectivity. Second, as an integral model to investigate various neurological

and psychiatric disorders, further investigation of the FIC connectivity in the triple networks in different diseases would contribute to better understanding of the mechanism of the mediatory function of this region. For instance, the VENs that are speculated to be the potential neuronal basis of the outflow hub of the FIC are found to be selectively targeted in fronto-temporal dementia but not in Alzheimer's disease (Kim et al., 2012; Santillo, Nilsson, & Englund, 2013) and autism (Kennedy, Semendeferi, & Courchesne, 2007). Using disease models to compare the differences of the FIC connectivity in different disorders is likely to provide a way to further verify the neuronal basis of the integral causal outflow hub played by the FIC. Third, it should be noted that different learning algorithms of BN have been deployed in recent connectivity studies (Gates & Molenaar, 2012; Iyer et al., 2013), but comparing results derived from different BN methods was beyond the scope of current article, which would however be methodologically interesting for future studies. Finally, we note that the correlations between FIC connectivity weights and cognitive performance in the exploratory examinations were not survived from multiple comparison corrections, suggesting this correlational effect was relatively small. A possible reason is that the connectivity was calculated during resting state, while cognitive performance was assessed during an independent period. In addition, the cognitive performance was derived from relatively limited number of cognitive domains. Therefore, it would be interesting for future studies to use task fMRI to further validate the cognitive correlations with FIC connectivity in the triple networks while performing various cognitive tasks.

To conclude, data-driven exploration and validation of regional directed connectivity of the triple network model demonstrates that the FIC acts as a crucial outflow hub that causally mediates activity of the DMN and CEN. Moreover, the mediating function of the FIC in the model is significantly related to individual ability in memory and executive function. The finding highlights the FIC as an important region worthy of research in future studies of network mechanisms of cognitive function and various neurological and psychiatric diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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