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Network Differential in Gaussian Graphical Models from Multimodal Neuroimaging Data*

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***Abstract*— Multimodal brain network analysis has the potential to provide insights into the mechanisms of brain disorders. Most previous studies have analyzed either unimodal brain graphs or focused on local/global graphic metrics with little consideration of details of disrupted paths in the patient group. As we show, the combination of multimodal brain graphs and disrupted path-based analysis can be highly illuminating to recognize path-based disease biomarkers. In this study, we first propose a way to estimate multimodal brain graphs using static functional network connectivity (sFNC) and gray matter features using a Gaussian graphical model of schizophrenia versus controls. Next, applying the graph theory approach we identify disconnectors or connectors in the patient group graph that create additional paths or cause absent paths compared to the control graph. Results showed several edges in the schizophrenia group graph that trigger missing or additional paths. Identified edges associated with these disrupted paths were identified both within and between dFNC and gray matter which highlights the importance of considering multimodal studies and moving beyond pairwise edges to provide a more comprehensive understanding of brain disorders.**

***Clinical Relevance*— We identified a path-based biomarker in schizophrenia, by imitating the structure of paths in a multimodal (sMIR+fMRI) brain graph of the control group. Identified cross-modal edges associated with disrupted paths were related to the middle temporal gyrus and cerebellar regions.**

I. INTRODUCTION

The advent of modern neuroimaging techniques has provided useful and insightful information regarding different brain disorders such as schizophrenia (SZ). SZ is a severe mental illness characterized by symptoms such as delusions, hallucinations, social withdrawal, and deficits in cognitive functions. The disconnection hypothesis in SZ was first raised by Friston and Frith [1] and associated with both structural [2] and functional [3] brain networks. SZ has varyingly been reported as a disorder of brain connectivity including hypo-connectivity [4], hyper-connectivity [5], and some studies reported as a dysconnectivity syndrome involving both hypo-connectivity and hyper-connectivity [6], [7].

The combination of neuroimaging techniques and graph theoretical approaches has enabled us to examine and understand these psychiatric brain disorders in a more quantitative way [8], [9], [10], [11]. Brain network analysis based on graph theory can offer key new insights into the structure and function of the brain network in SZ. In brain networks, nodes indicate brain regions, and the edges are regarded as some measure of structural or functional interaction between nodes. Once a brain network is established, graph theory can be used to describe and compare the overall topological patterns of the network through graph metrics such as clustering coefficient, modularity, average path length, etc. [12]. For example, graph metrics including path length and global efficiency have been shown to be disrupted in SZ [13].

However, most previous studies analyzed either unimodal brain graphs or focused on local/global graphic metrics with little consideration of details of disrupted paths in the patient group. In this study, we aim to identify disrupted paths on the multimodal brain graph of the patient group. Each modality provides a different but complementary view of brain function or structure [14]. There is considerable evidence of multimodal brain differences in SZ versus control groups [15], [16], [17], [18]. However, there are only a few studies in the context of a combination of multimodal neuroimaging data and graphical models and there is more to be studied in this area that may help to unify disparate findings in SZ. We leveraged prior work on path analysis [19] to identify edges associated with absent paths and additional paths in the patient group graph as the differences between control and patient groups are presumably the outcome of multilink disruptions in the paths. We aim to identify multimodal path-based biomarkers for individuals with SZ using the graph theory approach.

Moreover, for estimating the structural or functional connectivity, using Pearson's correlation coefficient is common practice in the literature. Although commonly used, Pearson's correlation does not distinguish whether two brain components are directly connected or indirectly connected through another brain component. To mitigate this, in this study, we use the Gaussian graphical model (GGM). GGM is

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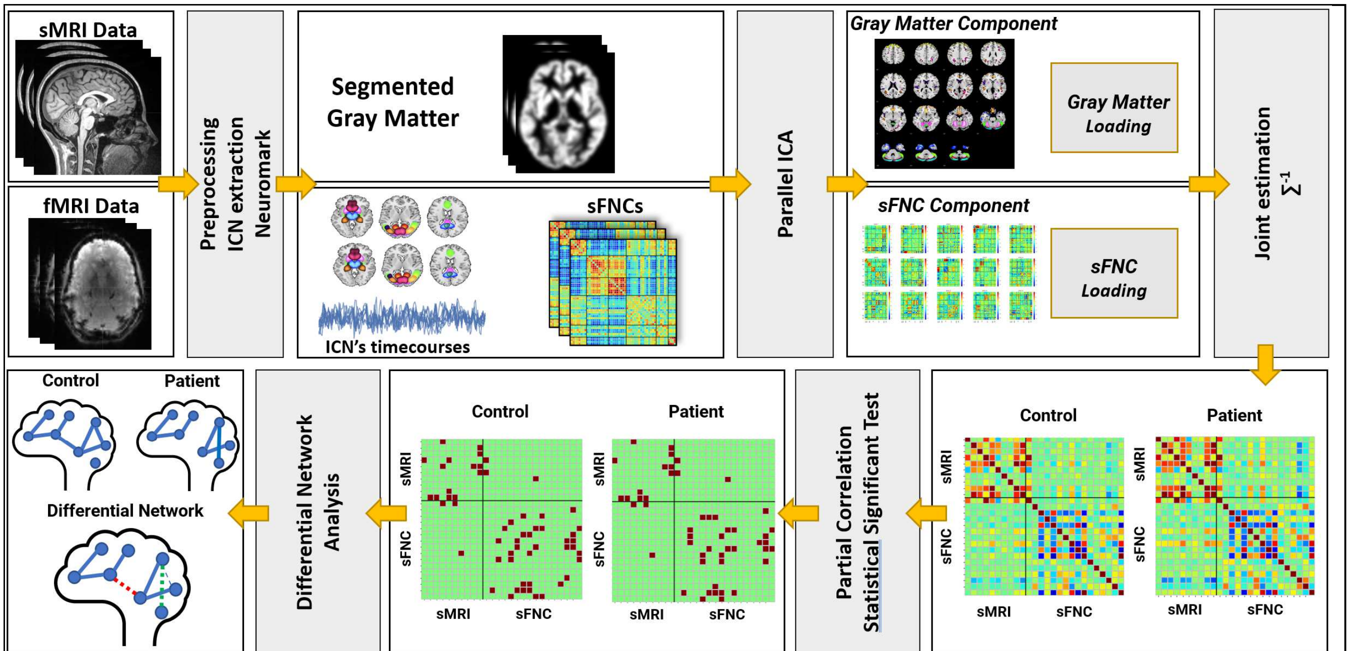

Figure 1. Method outline. sMRI and fMRI data were collected. Preprocessing steps were applied and sFNC and GM maps were estimated as input features. To estimate multimodal nodes for the brain network, pICA was performed as a data fusion algorithm. sFNC and gray matter components (nodes of multimodal brain graph) were calculated using the component matrices. To estimate multimodal edges, precision matrices were estimated for control and patient by applying the joint graphical lasso. Next, partial correlation matrices were calculated, and adjacency matrices were determined by applying the parametric test for the statistical significance of the partial correlation. Elements of the adjacency matrix are considered as one only where the corresponding false discovery rate (FDR) corrected p-value was significant ($p < 0.05$). Lastly, differential network analysis was performed to estimate edges associated with disrupted paths in the patient group.

a probabilistic graphical model based on partial correlation which is a correlation between the time series of two brain components after adjusting for the time series of all other brain components. we propose a way to build multimodal GGM for control and individuals with SZ in a data-driven way to define nodes and edges. We combine functional MRI (fMRI) and structural MRI (sMRI) data to improve neuromarker identification and to take advantage of multimodal cross-information.

The remainder of the paper is structured as follows. Section 2 describes the details of our proposed method. Section 3 provides the result of applying the path analysis algorithm on estimated multi-modal graphs of control and patient groups. We provide concluding remarks in Section 4.

II. MATERIALS AND METHOD

In this section, we first describe our approach to estimating multimodal brain networks of control and patient groups in a data-driven manner using GGM. Next, we analyze paths on the multimodal brain graphs of control versus control. Fig.1 illustrates the method steps in more detail.

A. *Data information, preprocessing, and feature extraction*

We considered data from the function Biomedical Informatics Research Network (fBIRN) study [20] that included sMRI and fMRI collected from 160 controls and 151 SZ patients. Written informed consent was obtained from all subjects. The fBIRN demographics can be seen in Table 1. Data preprocessing was performed using the SPM12, (http://www.fil.ion.ucl.ac.uk/spm/) toolbox followed by registration to the standard Montreal Neurological Institute (MNI) space. Voxel-level gray matter volume maps and fMRI time series were generated from the structural data and functional data, respectively. Next, a spatially constrained group-independent component analysis approach with the Neuromark pipeline [21] was applied to the functional data to obtain 53 consistent components corresponding to brain areas also known as intrinsic connectivity networks (ICNs). Fifty three ICNs categorized into seven functional domains include auditory, cerebellar, cognitive-control, default-mode, sub-cortical, sensorimotor, and visual. Subsequently, we calculated the static functional network connectivity (sFNC) matrix for each subject by computing pair-wise correlations using the entire length of the ICNs time course.

TABLE I. DEMOGRAPHICS OF FBIRN COHORT.

	Control	Schizophrenia
Number	160	151
Age	37.0±10.9	38.8±11.6
Gender	45F[a]/115M	36F/115M

a. F, female; M, male

B. *Estimating multimodal graphs using brain imaging data (GM and sFNC)*

To estimate a multimodal brain graph, we need to define multimodal nodes and edges. To estimate multimodal nodes, we used parallel ICA (pICA) as a data fusion algorithm. pICA is a hypothesis-free statistical technique that extends ICA to analyze two modalities to identify independent components from each modality and estimates the relationships between the two modalities [22]. After estimating sFNC and GM maps as input features, we applied pICA on these two features and set the number of components to fifteen which is within a reasonable range of previous studies (implemented in the FIT toolbox from TReNDS (http://trendscenter.org/software/fit)).

pICA generates four matrices including two loading matrices, one for each modality with the dimension of (number of

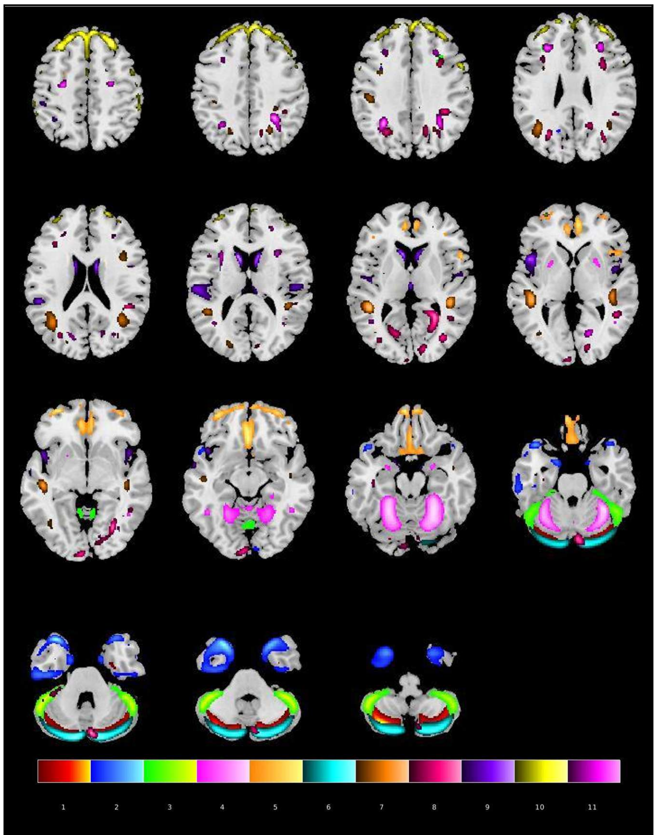

Figure 2. Eleven GM components estimated from the ICA analysis.

subjects: 311) × (number of components: 15), and two-component matrices with the dimension of (number of components: 15) × (number of GM voxels / sFNC measures).

Relying on expert knowledge we removed four artifactual components of GM maps. The plot of the remaining eleven components of GM maps can be seen in Fig.2. Fig.3 shows the sFNC maps in component-by-component matrix form (53×53).

After determining multimodal nodes, we used GGM to model the multimodal nodes interactions wherein edges demonstrate a partial correlation between multimodal nodes. The precision matrix (inverse of the covariance matrix) in GGM summarizes the conditional dependence of network structure that is, two nodes are conditionally independent, given all other nodes if and only if their corresponding off-diagonal entry of the precision matrix is zero and the graph structure can be inferred based on nonzero entries.

To estimate the precision matrix, we used the joint graphical lasso estimator [23] on the loading matrices for the control and patient group. We chose to use a joint estimation as growing evidence demonstrates that common structure across groups enhances the estimation power, especially for high-dimensional data [24]. Having the precision matrices for control and groups, we calculated the partial correlation matrices and applied a parametric test for the statistical significance of the partial correlation. We considered an edge between two brain components (nodes) only where the corresponding false discovery rate (FDR) corrected P-value was less than 0.05.

C. *Differential network analysis*

After estimating multimodal GGMs for control and patient groups, we then compared and analyzed paths between multimodal nodes of the control and patient group by leveraging prior work on path analysis [19]. We investigated cases where there is at least one path between two nodes in the control group graph, but they are not reachable from each other in the patient group which means there is no path between them in the patient group graph. We are looking for edges in

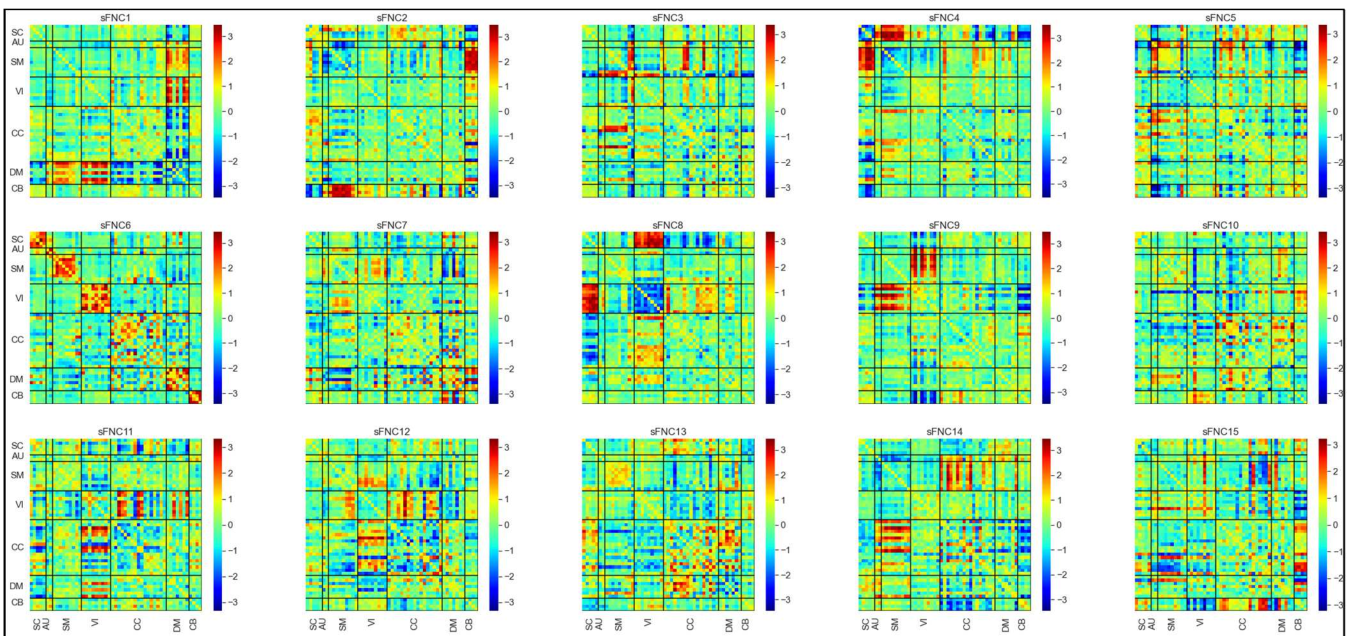

Figure 3. Fifteen sFNC in component-by-component matrix form.
(AU: auditory, CB: cerebellar, CC: cognitive-control, DM: default-mode, SC: sub-cortical, SM: somatomotor, VI: visual)

the patient group whose absence resulted in an absent path. We call this type of edge, a disconnector. Conversely, we explore cases where there is no path between two nodes in the control group graph, however, those two nodes are reachable from each other which means there is at least one path in the patient group graph. In this case, we are looking for additional new edges in the patient group graph that trigger new paths. We call this type of edge, a connector. In other words, disconnectors cause disconnection, and connectors cause abnormal integration in the patient group graph.

To address this, we use the concept of the connected component in graph theory. In a connected component, it is possible to get from every node to every other node through a series of edges, called a path [25]. In a brain graph based on GGM when two nodes are part of a connected component, we can conclude that they are conditionally dependent given all other nodes in a graph.

With reference to the path structure of the control group graph and using the concept of connected components in graph theory, we determined the disconnectors associated with absent paths and new edges (connectors) associated with additional paths in the patient group graph. First, we identify all connected components in the control graph, and if any of them are scattered into multiple connected components in the patient group, we determine the missing edges associated with disconnectivity (disconnector) by imitating the path structure of the control group. In addition, if any connected components in the patient group graph contain multiple connected components of the control group, we identify additional new edges (connectors) with reference to the structure of the path in the control group graph. Note, not all missing edges in the patient group trigger disconnection and likewise not all additional edges in the patient group trigger new connections. Fig. 4 illuminates the idea of identifying disconnectors and connectors in more detail.

III. RESULTS

Fig.3 summarizes the results of differential network analysis and identified disconnectors and connectors in the estimated multimodal brain graphs of the SZ group. Disconnectors associated with disconnection are shown as solid red edges and simple missing edges are shown with the dashed red line. Two disconnectors and four connectors were observed, within and between modalities. One disconnector and two connectors were identified between sFNC and GM modalities.

The cross-modal disconnector is between sMRI_3 and sFNC_4, and another one is within the sFNC modality, that is between sFNC_4 and sFNC_3. A cross-modal missing edge is between the cerebellar component and the sFNC feature which has a negative correlation between cerebellar and sub-cortical domains and has high functional connectivity in the somatomotor domain. Regarding connectors, we identified two cross-modal connectors (sMRI_9, sFNC_7) and (sMRI_9, sFNC_8) and two connectors within the modalities which are (sFNC_1, sFNC_10) and (sMRI_10, sMRI_15).

The connectors are shown with a solid green line in Fig.3. One of the cross-modal connectors is between the middle temporal gyrus component and the sFNC _7 feature which has high functional connectivity between the default mode and the

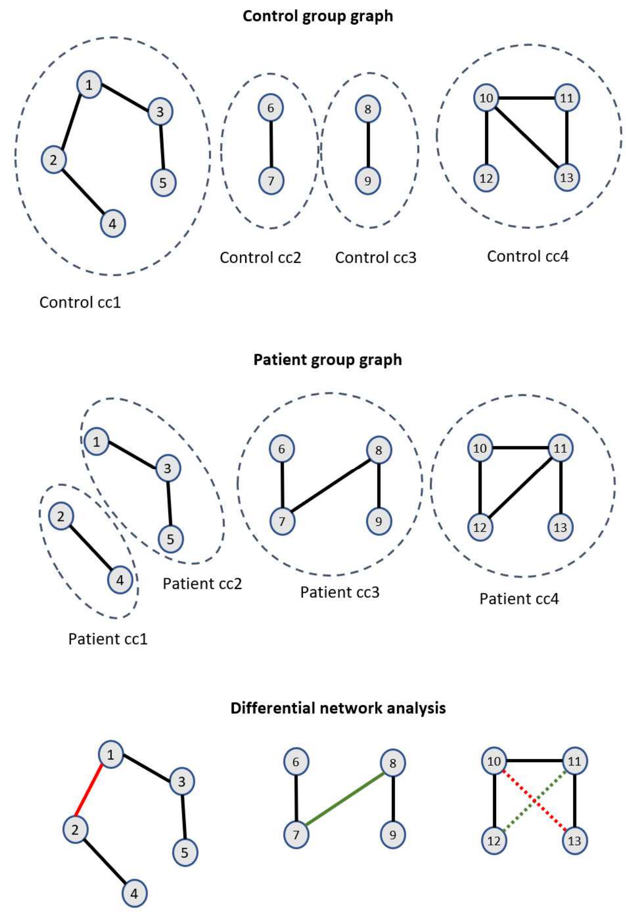

Figure 4. The first row is an example of the control group graph that includes four connected components (Control cc1, Control cc2, Control cc3, and Control cc4). The second row is an example of the patient group graph that has a different structure in comparison with the control group and it includes four connected components. There are some missing and additional edges in the patient group graph in comparison with the control group graph. The goal is to identify edges that trigger disconnection or abnormal integration in the patient group by mimicking the graph structure in the control group. The nodes of "Control cc1" are {1, 2, 3, 4, 5}and they are all reachable from each other in the control group graph. However, these nodes belong to two separated connected components in the patient group graph: "Patient cc1" and "Patient cc2". There is no path between the nodes of two separated connected components. Edge (1,2) as shown with red color in the third row, will be considered as a disconnector as it creates the disconnection. On the contrary, nodes {6, 7, 8, 9} belong to the one connected component in the patient group graph "Patient cc3". However, the structure in the control group graph is different and they belong to two separated connected components. Edge (7,8) which is shown with green color in the third row, will be considered as a connector as it created an abnormal integration in the patient group graph. Note, not all missing edges are associated with disconnection, and not all new additional edges are associated with an abnormal integration. For example, nodes {10, 11, 12, 13} belong to one connected component in a control group graph which is "Control cc4". In the patient group graph, these nodes are still part of one connected component which is "Patient cc4". Although edge (10,13) is a missing edge in a patient group graph it does not create a disconnection as they are still part of one connected component and reachable from each other. Edge (11,12) is a new edge in a patient group graph, but it does not create a new connection in comparison with the control group graph. The simple missing edge and simple additional edge are shown with a dashed red line and dashed green line in a third row, respectively.

cerebellar domains and another cross-modal connector is between the middle temporal gyrus component and the

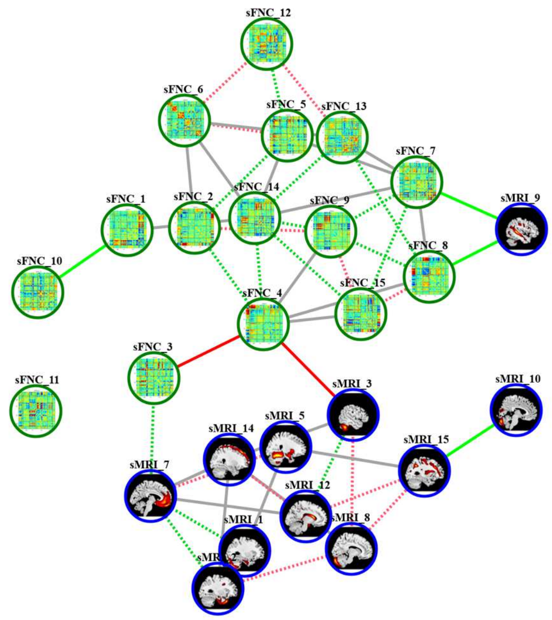

Figure 5. Disconnectors associated with disconnection are shown as solid red edges and additional edges associated with abnormal integration are shown with solid green edges. The simple missing and additional edges shown with dashed red and green line, respectively. Results show two disconnectors and four connectors both within and between modalities. One of disconnectors and two of connectors were observed between modalities.

sFNC_8 feature which has high functional connectivity between the visual and subcortical domains and weaker functional connectivity within the visual domains. Two within modality connectors are (sFNC_1, sFNC_10) and (sMRI_10, sMRI_15).

IV. Discussion

In this study, we presented an approach to assess multi-step graphical paths that span multimodal neuroimaging data. We aimed to identify multimodal path-based biomarkers for individuals with SZ, however, the proposed method can be applied to any undirected graph estimated from data related to other conditions as well. We proposed a method to estimate multimodal graphs of controls and patients with SZ in a data-driven manner. We defined data-driven nodes and edges. We used pICA for defining multimodal nodes and applied test statistics for determining edges. This reduces the bias of choosing an ad-hoc threshold for edge estimation of graphs.

We used GGM to model the human brain as GGMs are powerful tools for expressing statistical relationships between nodes. Bivariate correlation network analysis might result in many spurious edges as correlation cannot distinguish between direct and indirect associations. In contrast, relationships estimated by GGMs reduce the risk of identifying spurious relationships as it is a key advantage of partial correlations that reflects conditional independencies [26]. Path analysis on the estimated multimodal GGMs of control and SZ groups revealed two disconnectors and four connectors associated with disconnections and abnormal integrations, respectively. We identified several missing and additional edges that did not contribute to disconnections or abnormal integrations (dashed red and green edges in Fig. 5) that indicate the importance of analyzing paths than focusing on edges differences between groups of control and patient.

In this study, we employed two distinct neuroimaging modalities (sMRI and fMRI) to specifically investigate function-structure interrelationships. One of the disconnectors and two connectors were identified between modalities that demonstrate the importance of considering multimodal information and moving beyond pairwise edges to provide a more comprehensive understanding of brain disorders. The number of studies analyzing multimodal probabilistic graphical models is remarkably small as it necessitates broader proficiency in collecting multimodal data, analyzing, modeling probabilistic graphical models, and interpreting the outcome in comparison with unimodal studies. The multimodal study's findings can be complementary to and extend the unimodal analysis. Interestingly, two cross-modal connectors that we identified are related to the middle temporal gyrus (sMRI_9, sFNC_7) and (sMRI_9, sFNC_8)). sMRI_9 indicates middle temporal gyrus and persistently previous studies have reported middle temporal gyrus abnormalities in SZ [27], [28], [29], [30]. The cross-modal disconnector (sMRI_3, sFNC_4) that was identified as associated with the cerebellar component (sMRI_3) and the sFNC feature which has a negative correlation between cerebellar and sub-cortical domains and has high functional connectivity in the somatomotor domain. Abnormalities related to cerebellar dysfunction in SZ have been reported numerously [31], [32], [33]. Therefore, in light of previous works in SZ, it seems our result obtained by analysis of the path on multimodal neuroimaging data is consistent, but we also observed new relationships that need future work replicating the results in additional datasets and applying different modalities and features. There were more identified connectors than disconnectors, which might be related to a brain compensatory response in the SZ group. This should be investigated further in a future study.

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