Different Features of Metabolic Connectivity Map and Granger Causality Method in Revealing Directed Dopamine Pathways: A Pilot Study Based on Integrated PET/MR

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Abstract

Granger causality (GC) analysis and metabolic connectivity map (MCM) are two effective connectivity (EC) methods commonly used in functional brain researches. Although they have a common basis in central neurophysiology, their differences in depicting EC are not clear because of absences of data acquired simultaneously and exactly aligned. Integrated positron emission tomography and magnetic resonance image (PET/MR) technology makes this available. Using the “Monash rs-PET/MR” dataset obtained from the OpenNeuro database, we first conducted GC and MCM analysis of the brain dopamine reward circuit, a well-known system mainly consisting of the bilateral Orbital Frontal Cortex (OFC), Caudate (CAU), Nucleus Accumbens (NAc), Thalamus (THA) and Substantia Nigra (SN). Then, we validated their ability of describing EC to priori knowledge. The significance of each directed pathways within group were tested through one-sample t-test (for MCM) or Wilcoxon test (for GC), the significance level was set at $p < 0.05$ after FDR correction. Three types of connections were found: the cortico-nucleus (long-range), the nucleus-nucleus (neighborhood) and the symmetrical connections. GC revealed long-range connections including OFC-CAU and OFC-NAc; MCM revealed neighborhood connections including NAc-CAU, SN-THA, and THA-CAU, the symmetrical connections including the bilateral NAc, CAU, THA, as well as OFC-CAU. Thus, different patterns in directional networks of dopamine reward circuit revealed by GC and MCM. GC predominated at aspects of cortico-nucleus bidirectional connections, while MCM of directed connections among close regions and symmetrical regions. This study implicates that research involving in effective connections should choose an appropriate analysis method according to the study purpose.

Highlights

- This is the first comparative study on effective connectivity methods based on integrated PET/MR data
- Different features were found of depicting directed dopamine pathways between metabolic connectivity map and granger causality

1. Introduction

The human brain has long been recognized as a continuously communicating network[1]. The multi-scale intrinsic activities, as small as neurons to brain regions, could be analyzed with functional connectivity (FC) to form the functional brain network. However, the networks built from correlation has no direction information. The effective connectivity (EC), which gives the directional or causal relationships among brain regions is more important for the exploration of the underlying brain mechanisms[2]. The understanding of the directionality of brain networks provides insights into the diagnosis and treatment of neurological or mental diseases such as Alzheimer’s disease[3], schizophrenia[4] and addiction[5] etc.

Granger causality(GC) analysis is a commonly used approach in functional MRI studies to reveal the directionality between brain regions[6]. GC was originally introduced and operationalized by Wiener and

Granger in economics[6], though linear vector autoregressive (VAR) model of stochastic time series data. The order of VAR model is usually determined by Bayesian information criterion (BIC) theory[2,5,7]. The basic concept of GC is that if the past of time series X can be used to facilitate the prediction of the future of the time series Y, then we say there is a Granger causal influence from the X to Y. GC method has been used broadly in neuroscience in the past decade, such as opioid addiction, migraine without aura, obsessive-compulsive disorder and [5,8,9].

Metabolic connectivity map (MCM)[10] analysis is a novel approach to reveal the metabolic directionality among brain regions, using simultaneously collected positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) data. This method is based on the concept of energy consumption in neuronal communication. Most energy metabolism is dedicated to signaling and is consumed up to 75% at the target neurons, post-synaptically [10][11–14]. Riedl et.al scaled this to the systems level, and assumed that an increase in local metabolism reflects an increase in afferent effective connectivity from source regions. They further hypothesized that the spatial correlations between metabolic activity and FC represents this EC spatial profile [10]. In other words, the MCM reflects the concordance between improved glutamate consumption pattern and the improved blood oxygen level dependent (BOLD) correlation pattern at the target region. As a novel and promising approach, MCM has been used in identifying the altered EC within default mode network for patients with Alzheimer's disease [3], in revealing the stable bidirectional connection between early/higher visual regions of healthy cohorts[10], and in studying the cognition task-induced reconfiguration of whole-brain networks[15].

The GC identifies the directional connectivity through the predictive relationship between BOLD signals while the MCM identifies this by the association between glucose metabolism and the FC. Since the level of glucose metabolism and the level of the BOLD signal are both influenced by the same cerebral blood flow, the two methods share a common basis in central neurophysiology. However, little has been known about the differences in depicting effective connectivity between GC and MCM due to the absencing fMRI and PET data acquired simultaneously and aligned exactly.

Dopamine (DA) plays several important roles in the human brain and has been researched for decades. The DA reward system has been well researched and described and is therefore suitable for the purpose of this comparative methodological study. Reward circuits mainly involves substantia nigra (SN), ventral tegmental area (VTA), thalamus (THA), ventral striatum, dorsal striatum and prefrontal cortex[16,17]. Three pathways consist the reward system: the nigrostriatal pathway, along which the SN sends a dopaminergic projection to the dorsal striatum; the meso-limbic pathway, where the VTA sends a similar type of dopaminergic projection to the NAc; the meso-cortical pathway, where the dopaminergic projections from SN/VTA through THA to prefrontal cortex[18,19]. Besides the dopaminergic projections, there are also GABAergic projections and glutamatergic projections among these DA areas, performing the inhibitory or excitatory functions[20].

With the development of integrated PET/MR technology, there is opportunity to compare GC and MCM using the same dataset. Although GC has a wider scale analysis ability from voxel-wise to regions-of-

interest (ROI-wise), in contrast the MCM could only be applied to ROI-wise effective connectivity inference due to methodology issue currently. Thus, an ROI-wise effective connectivity analysis was used in this study. Based on the simultaneously collected PET and MRI data from a group of healthy participants, this exploratory study aims to reveal the sensitivity and consistency of the GC and MCM methods in identifying the directed pathways between brain regions. We assumed that both approaches could reveal important effective connectivity consistent with the DA pathway, but may not share the same pattern:

2. Materials And Methods

2.1 Datasets

The data of this study were obtained from the Monash rsPET-MR dataset[21–24] in the OpenNeuro database (<https://doi.org/10.18112/openneuro.ds002898.v1.1.1>). It is a simultaneous fMRI-fPET dataset acquired from young, healthy individuals at rest. Here is a brief description of this dataset: Participants (n=27, 21 female) were all right-handed, 18 to 23 years in age (mean 19 years), and 13 to 18 years of education (mean 14 years), and no history of diabetes, diagnosed Axis-1 mental illness or cardiovascular illness[21]. Participants underwent a 95-minute simultaneous MR-PET scan in a Siemens (Erlangen) 3 Tesla Biograph molecular MR scanner (Syngo VB20P). ^{18}F -fluorodeoxyglucose (FDG; average dose 233MBq) was infused over the course of the scan[21]. Over the first 30-mins following infusion onset, T1 3D MPRAGE (TA = 7.01 mins, TR = 1640ms, TE = 2.34 ms, flip angle = 8° , FOV = $256 \times 256\text{mm}^2$, voxel size = $1 \times 1 \times 1\text{mm}^3$, 176 slices; sagittal acquisition); For the remainder of the scan, six consecutive 10 min blocks of T2*-weighted echo-planar images (EPIs) were acquired (TR = 2.45s, TE = 30ms, FOV = 190mm^2 , $3 \times 3 \times 3\text{mm}^3$ voxels, 44 slices, ascending axial acquisition)[21]. More details could be reviewed in previous paper[21,23].

2.2 Image Preprocessing

The first 10 min block BOLD data and the corresponding 10 min FDG PET data were used in this study, as well as the T1 3D MPRAGE data for structural segmentation and registration. According to the scan protocol[21], the PET data were reconstructed every 16 seconds to a volume, and the corresponding 10 min data should be volume number starting from 129 to 165 for each participant. These PET volumes were extracted and averaged to get the static FDG PET image.

CONN[25] toolbox (version 20.b) was used for BOLD data preprocessing. It is a functional connectivity toolbox based on the Statistical Parameter Mapping 12 toolbox (SPM, <http://www.fil.ion.ucl.ac.uk/spm>). The default preprocessing pipeline for volume-based analyses (direct normalization to MNI-space) was utilized, including the following steps: Realignment and unwarp, slice timing correction for inter-slice differences in acquisition time, ART-based outlier detection (https://www.nitrc.org/projects/artifact_detect) to identify outlier scans for scrubbing, segmentation functional image and anatomical images to gray/white matter and cerebrospinal fluid (CSF) tissue classes using SPM unified segmentation and normalization procedure, and normalize to 2mm

(functional) or 1mm (anatomical) isotropic voxel size in MNI space. Finally, the functional images were smoothed using spatial convolution with Gaussian kernel of 4mm full width half maximum (FWHM). After preprocessing, functional data were further denoised using CONN's denoising pipeline, removing potential confounding effects in the BOLD signal such as noise components from white matter and CSF areas[26], estimated subject-motion parameters, scrubbing and session effects[27]. Temporal frequencies below 0.008 Hz or above 0.09 Hz are removed from the BOLD signal in order to focus on slow-frequency fluctuations while minimizing the influence of physiological, head-motion and other noise sources[28].

2.3 ROI Definition and FC Analysis

FSL[29] built-in atlases were used to generate 10 ROIs in dopamine system. Eight bilateral ROIs were extracted from Harvard-Oxford probability atlas, thresholded at 50% probability, and then binarized into masks. These ROIs were thalamus (THA), nucleus accumbens (NAc), caudate (CAU) and orbital frontal cortex (OFC), bilaterally. Talairach Daemon atlas was used to generate bilateral substantia nigra (SN) ROI masks directly. For each participant, we calculated the ROI-wise and voxel-wise functional connectivity of every ROI, forming one FC matrix and 10 FC maps per participant. The element value in FC matrices and voxel value in FC maps were further transformed to z-value utilizing Fisher's r to z transformation equation, thus the distribution of z-value would approximately be normal. For ROI-wise FC matrices, one sample t-test was utilized to determine significant FC pathways within participant group. The significance level was defined by $p < 0.05$, after false discover rate (FDR) multiple comparison correction.

2.4 Granger Causality Analysis

The granger causality indices (GCI) of each ROI pairs were calculated along each significant FC pathways. This GCI was calculated using autoregressive model:

$$Y_t = \sum_{k=1}^p b_k Y_{(t-k)} + cZ_t + \varepsilon_t$$

And the joint regressive representation was:

$$Y_t = \sum_{k=1}^p a_k X_{(t-k)} + \sum_{k=1}^p b_k Y_{(t-k)} + cZ_t + \mu_t$$

$$F_{x \rightarrow y} = \ln \frac{\text{var}(\varepsilon_t)}{\text{var}(\mu_t)}$$

Here, Y_t and X_t are the preprocessed ROI signals, ε_t and μ_t represents the residuals of autoregression and joint regression, p means the lag of autoregression model. $F_{x \rightarrow y}$ is the GCI value defined as the granger causality effect from ROI_x to ROI_y , so each ROI pair has two GCI value, representing GC effect of two directions. According to Bayesian information criterion[5], the lag of vector auto-regression model was determined to be 2.

While the distribution of GCI was not clear, the one sample t-test of group GCI statistical which needs the normal distribution assumption may not be appropriate. To get the real distribution of GCI, permutation-based technology was adopted. We randomly switched ROI signals among participants preprocessed BOLD data, then calculated the GCI values of each ROI pairs, and repeat this procedure for 100,000 times. Finally, this generated a simulated GCI null distribution for real datasets. To test the significance of group GCI, the non-parametric one-sample Wilcoxon signed rank test was utilized. If the GCI value of one directional connection was significantly higher than the median value of GCI null distribution, this directional connection should be considered significant ($p < 0.05$, FDR corrected).

2.5 Metabolic Connectivity Map (MCM) Analysis

Static FDG-PET images were preprocessed using FSL, including registration and normalization to 2mm voxel size MNI space. Standard uptake value ratio (SUVr) maps were converted by dividing the mean value of reference region. According to previous research[30,31], cerebellum gray matter was chosen as the reference region. With regard to high-resolution PET data acquisition, there was less need to perform partial volume effect correction. The normalized SUVr maps and BOLD data of each participants were used to calculate MCM[10]. The MCM value of seed ROI X to target ROI Y was calculated as follows, the same method in the research of Riedl et.al [3,10]:

$$MCM_{X \rightarrow Y} = Correlation(FC_{Y|X}, FDG_Y)$$

In the formula, FDG_Y is the voxel-wise profiles in ROI Y, representing the neuronal activity in ROI Y; $FC_{Y|X}$ is the voxel-wise FC in ROI Y while ROI X as the seed ROI, representing the correlation between each voxel time series in ROI Y and the cluster time series of ROI X; The spatial correlation between FDG and FC voxel-wise profiles is the MCM value which represents the metabolic effective connectivity from ROI X (seed) to ROI Y (target).

Based on the cellular model of neuro-energetics, a positive $MCM_{X \rightarrow Y}$ value identifies the signaling input along the FC pathway from ROI X to ROI Y. To identify the significant MCM connections among participant group, one-sample t -test were conducted for MCM values along each direction of FC pathways. The significance level was set at $p < 0.05$, FDR corrected.

3. Results

3.1 FC Analysis

Among participants group, FC existed between most of the ROI pairs. The FC pathways connecting bilaterally symmetrical brain structures were significant for all ROIs, which were the FC between bilateral CAU, bilateral NAc, bilateral OFC, bilateral THA and bilateral SN. Besides, the FC between left SN and bilateral CAU, bilateral NAc, bilateral OFC, the FC between right SN and left CAU, bilateral NAc, left OFC,

and the FC between right THA and bilateral OFC were not significant. All other FC between ROI pairs were significant except above mentioned pathways (Fig.1, One-sample t -test, $p < 0.05$, FDR corrected).

3.2 GC Analysis

The distribution of GCI after 100,000 times simulation was shown in Fig.2. The GCI density curve was not normal but skewed, with a median value at 0.0163. The μ parameter in Wilcoxon signed rank test thus was set as 0.0163, and if the GCI was significantly higher than μ , the corresponding GC connection was considered significant. After multiple comparison correction, significant GC connections were as follows: a bidirectional connection between left NAc and right OFC and eight significant unidirectional connections respectively from right THA to left CAU, from left CAU to right CAU, from left CAU to left OFC, from left NAc to left CAU, from right OFC to left CAU, from left OFC to right CAU, from right NAc to left OFC, and from left OFC to right OFC (Fig.3, One-sample Wilcoxon signed rank test, $p < 0.05$, FDR corrected).

3.3 MCM Analysis

The significant MCM connections layover FC pathways were as follows: 3 bidirectional connections respectively between bilateral THA, between left CAU and left NAc, and between right CAU and right NAc, and 7 unidirectional connections respectively from left SN to right THA, from right OFC to right CAU, from left OFC to bilateral CAU, from right NAc to bilateral CAU, and from left CAU to right CAU. (Fig.4, One-sample t -test, $p < 0.05$, FDR corrected)

4. Discussion

In this present study, GC and MCM methods were applied to show differences in identifying the directional connectivity of brain reward system based on PET/MR dataset. Our findings demonstrated that GC was predominated at aspects of cortico-nucleus bidirected connections of reward system, while MCM of directed connections among adjacent regions and symmetrical region. Each of the two methods has its own features, and researchers should carefully choose them before starting analyzing.

Both GC and MCM identified some of these modulation pathways in DA systems, but with different patterns. According to our findings, GC did well in identifying long-range connections (cortico-nucleus). The bidirected connections between striatum to OFC were identified by GC, which is consistent with the meso-cortical pathway in reward circuits[32]. On the contrary, MCM did well in identifying directed connections among nearby brain areas (nucleus-nucleus) and among symmetrical brain areas. These tightly connections imply the frequent communications between dorsal and ventral striatum and also the intense communications between bilateral subcortical brain areas in resting state brain. The reason for these significant differences between GC and MCM may come from the deep nature of the two methods. GC's principal is based on temporal predictability of future activity from knowledge of past activity[33]. What GC revealed in the studies should be interpreted as predictions between time series[2]. If timeseries X and Z is highly correlated to each other (in other words, high FC between X and Z), this high FC would

cause lower GC between X and Z, because GC uses lag to predict between timeseries, not correlation. According to GC's algorithm, an extreme example is that when X and Z is the same, there is obviously no GC effect at all. In our results, the FC between bilateral THA got highest value, but there was no significant GC pathway between bilateral THA. Besides, very high FC tends to get a lower GC, while this High-FC effect does not affect MCM. MCM's algorithm uses the voxel-wise spatial pattern similarity between FDG and FC to generate ROI-wise causality effect[3,10]. The nearby brain regions and symmetrical brain regions often have higher FC than long-distance brain regions. This may be the methodological reason that caused GC to give less results than MCM in nucleus-nucleus (nearby regions) pathways and symmetrical region pathways, as well as GC to give better results than MCM in cortico-nucleus (long-range) pathways. Although this inference is suggested by both the observed phenomenological and algorithmic differences, more stringent experiments are needed to verify this.

When the subtentorial areas were involved, MCM methods reported poor results and GC had even worse results. Only MCM identified the important projections from SN to THA, and the information interaction pathways between bilateral THA. The SN and THA were totally isolated from cortical and striatum according to our results, but the SN and THA should have interactions with cortical areas and striatum. This deficiency here may come from many factors. The first one could be the susceptibility of mid-brain/brainstem areas to signal loss and image distortion for BOLD signals[34]. This reason explains why GC works even worse there. Due to GC's nature, it relies heavily on the BOLD signal quality. This disadvantage may have less effect for PET data. MCM got some benefit from high-resolution PET images than GC. Another factor may come from the lack of accuracy of the SN ROI template, considering the fact that SN is located in the mid-brain and is more likely to have poor registration results than cortex area using regular normalization procedure[34]. Besides, the correction method might be too stringent in our One-sample statistics when comparing to other studies which only focused on group differences on effective connectivity. For example, most of the GC studies calculated the between-group GC differences other than within-group patterns, so they could simply test whether the group differences were significantly not equal to zero. When we focused on within-group patterns of GC, we had to choose a more stringent value to test. This strategy may eventually cause less survived results. MCM, on the other hand, got less influence than GC when doing within-group analysis, and the results in subtenorial areas was better than GC.

This study has some limitations. Firstly, the reward circuit involved ROIs in this study was arbitrary selected and thus may cause the results less comprehensive. Secondly, the scan protocol of Riedl's study[10] was to acquire a 10min BOLD sequence right after the FDG injection and the PET data used in MCM analysis was collected 30 min after injection. While our dataset obtained from OpenNeuro acquires BOLD sequences 30 min after injection, which was not the same with Riedl's study[10]. It should be pointed out that in our study, the PET data represents the cumulated regional energy demands before the fMRI acquisition window, while the fMRI data reflects the neuronal dynamics during the acquisition phase. In theory, we could assume that the resting-state brain would have similar activities across sessions, thus the FC should not change a lot, which assures the MCM's stability. Whether MCM changes or not during resting-state in different sessions was not clear, thus further research is needed. Third, there

are researches[1,35,36] providing improvements to original GC method, these variants claimed to be more reliable, but were not included in this study. These limitations remind us of the need for more cautious interpretation of results.

5. Conclusion

Both GC and MCM have their own features. Our results show that GC and MCM may reveal different patterns in directional networks. GC predominated at aspects of identifying long-range bidirected connections, while MCM of directed connections among adjacent regions and symmetrical regions. Poor connections in subtenorial areas were identified by both methods, but MEC got benefits from the compensation of the high-resolution PET data and worked better than GC. This implies that future research on effective connections requires an appropriate selection of methods to be conducted according to different objectives.

Declarations

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Conflicts of interest/Competing interests:

The authors declare that they have no conflict of interest.

Availability of data and material:

Openneuro.org, ds002898, open accessed at <https://doi.org/10.18112/openneuro.ds002898.v1.1.1>

Code availability:

Custom code based on open source software. Questions regarding the code implemented in this work can be addressed to the corresponding author.

Author's contributions:

Lei Wang and Longxiao Wei contributed equally.

Menghui Yuan and Yarong Wang are the co-corresponding authors

Ethics approval:

Not applicable. All data from open accessed datasets from Openneuro.org.

Consents to participate:

Not applicable.

Consent for publications:

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Clinical Trial Registration:

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Figures

Figure 1

The Group-level FC matrix shows that the bilaterally CAU, NAc, OFC and THA ROIs were significantly connected to each other. The SN and were significantly connected to THA. Color represents the z-transformed FC strength between ROI pairs. White color means statistically not significant. (One-sample t-test, $p < 0.05$, FDR corrected) CAU: Caudate, NAc: Nucleus Accumbens, OFC: Orbital Frontal Cortex, SN: Substantia Nigra, THA: Thalamus

GCI density curve

Figure 2

The GCI density curve. This curve comes from permutation-based technology to simulates real data GCI distribution with 100,000 times permutation. The distribution was a skewed curve, with 0.0163 as the median value, which is more appropriate than mean value for one-sample test in this situation.

Figure 3

The group-wise directional network identified by Granger causality. Arrows represent the direction of the pathways. The line thickness represents the relative strength of the granger causality index of that pathway. Bidirectional connection was identified between the right OFC and left NAc. (One-sample Wilcoxon signed rank test, $p < 0.05$, FDR corrected) CAU: Caudate, NAc: Nucleus Accumbens, OFC: Orbital Frontal Cortex, SN: Substantia Nigra, THA: Thalamus, L/R: Left / Right

Figure 4

The group-wise directional pathways identified by Metabolic effective connection (MEC) method. Arrows represent the direction of the pathways. The line thickness represents the relative strength of the MEC. There were more bidirectional interactions between NAc and caudate, and the unidirectional pathway from OFC to caudate revealed the regulation in frontostriatal dopamine pathway. (One-sample t-test, $p < 0.05$, FDR corrected) CAU: Caudate, NAc: Nucleus Accumbens, OFC: Orbital Frontal Cortex, SN: Substantia Nigra, THA: Thalamus, L/R: Left / Right