

Voxel-wise Intermodal Coupling Analysis of Two or More Modalities using Local Covariance Decomposition

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02 January, 2022

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1 CRediT author statement

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2 Abstract

When individual subjects undergo imaging with multiple modalities, biological information is present not only within each modality, but also between modalities - that is, in how modalities covary at the voxel level. Previous studies have shown that the covariance structures between modalities, or intermodal coupling (IMCo), can be estimated between two modalities, and that two-modality IMCo reveals otherwise undiscovered patterns in neurodevelopment as well as other processes. However, previous IMCo methods are based on the slopes of local weighted linear regression lines, which are inherently asymmetric and limited to the two-modality setting. Here, we present a PCA-based generalization of IMCo regression which uses local covariance decompositions to define a symmetric, voxel-wise coupling coefficient valid for two or more modalities. We then use this method to study coupling between cerebral blood flow, resting state activations, and functional connectivity in 803 subjects between ages 8 and 23. We demonstrate that coupling is spatially heterogeneous and varies with respect to age and sex over the course of neurodevelopment. As availability of multi-modal data increases, PCA-based IMCo offers a natural approach for summarizing relationships between multiple aspects of brain structure and function. An R package is provided.

3 Introduction

There is increased availability of multi-modality neuroimaging data on individual subjects, where each modality contains unique information about brain structure or function [TOCITE]. Such data allow us to explore patterns in individual modalities and how patterns in individual modalities relate to each other. In addition to these comparisons, multi-modal data allows us to observe the local covariance structure, or intermodal coupling (IMCo), between modalities (???). This local covariance structure can be interpreted as how modalities relate with respect to one another at the voxel level in individual subjects.

Previous studies have shown IMCo analysis is complementary to single-modality analysis and unveils otherwise undetectable findings [TOCITE]. For example, in neurodevelopment, IMCo between cortical thickness and sulcal depth has suggested the cortical sheet is generally thinner in sulcal locations when compared to gyral locations, though this relationship was more spatially heterogeneous than previously described (?). Additionally, this study showed the strength of coupling was lower in males compared to females and decreased with age. A separate study exploring IMCo between cerebral blood flow and amplitude of low frequency fluctuations (ALFF) showed that age-related declines in neurovascular coupling occurred most drastically during mid-adolescence and were enriched in the dorsal attention network (?). There were also differences in CBF-ALFF coupling between males and females; these differences were enriched in the frontoparietal network. In multiple sclerosis, IMCo has also shown use as a data augmentation tool to improve predictive accuracy of an automated lesion detection model over models using individual modality data alone (??).

In these prior studies, each voxel-wise coupling value was defined as the slope of the weighted regression lines fit within a local neighborhood between two modalities. However, since this method of calculating IMCo is based on regression slopes, it does not take into account voxel-level correlation and also suffers from inherent asymmetry, where coupling values depend on the order in which modalities are listed. For example, depending on which modality is the reference modality, a coupling value, m , will change to its inverse, $1/m$; this issue is especially problematic for coupling values with very small or very large magnitudes. Thus, this asymmetry necessitates arbitrary, yet influential, decision-making when it comes to analysis and inhibits straight-forward interpretation. Such a measure for IMCo is also limited to only two modalities, so the study of coupling between more than two modalities would require analysis of all pairwise coupling maps. As the number of total modalities increase, this can quickly become overwhelming to interpret.

We propose a novel, principal component analysis (PCA) based method for estimating IMCo that uses local covariance decomposition to define symmetric voxel-wise coupling values valid for two or more modalities that reduce the complex local covariance structures into a single value. Thus, our approach provides a more natural and interpretable way of describing coupling in settings with two modalities and allows for simplified study of overall local covariance structure in settings with more than two modalities. To demonstrate its sensitivity to biologically relevant patterns, we show PCA-based IMCo uncovers differences in three-modality coupling with respect to age and sex throughout neurodevelopment.

4 Methods

4.1 Subjects

We included 803 subjects (340 males) from ages 8-23 (mean = 15.6; sd = 3.3) from the Philadelphia Neurodevelopmental Cohort (PNC) (?). Of the 1445 PNC subjects who underwent neuroimaging, we initially excluded those meeting any of the following criteria: history of psychoactive medication (n = 165), history of inpatient psychiatric hospitalization (n = 51), or history of medical disorders that could impact brain function (n = 166). From the remaining 1113 subjects, we included those who underwent the combination of T1-weighted MRI, arterial spin labeling MRI (ASL), and resting state fMRI (rfMRI) scanning, each of acceptable image quality as determined based on automated and manual screening. This resulted in the final set of 803 subjects used for this study.

The Institutional Review Boards of the University of Pennsylvania and the Children’s Hospital of Pennsylvania approved all study procedures. All study subjects gave informed consent; for subjects under the age of 18, parents or guardians provided consent and subjects provided assent. Additional details of the PNC study have been previously described (?).

4.2 Image acquisition

All PNC imaging was acquired using a single 3T Siemens Tim Trio scanner with a 32-channel head coil. To minimize motion, subject heads stabilized using one foam pad over each ear and one over the top of the head. Image acquisition procedures have been previously described (?).

T1 structural images were used for alignment of all scans into common space. T1 images by 3D-encoded magnetization-prepared, rapid acquisition gradient echo (MPRAGE) T1-weighted sequence with the following settings: $T_R = 1810$ ms; $T_E = 3.51$ ms; FoV = 180×240 mm; matrix size = 192×256 ; number of slices = 160; slice thickness = 1 mm; inter-slice gap = 0 mm; resolution = $0.9375 \times 0.9375 \times 1$ mm. Cerebral blood flow (CBF) was estimated from a 3D-encoded spin-echo pseudo-continuous arterial spin labeling (pCASL) sequence with the following settings: $T_R = 4000$ ms; $T_E = 15$ ms; FoV = 220×220 mm; matrix size = 96×96 ; number of slices = 20; slice thickness = 5 mm; inter-slice gap = 1 mm; resolution = $2.3 \times 2.3 \times 6$ mm; 80 volumes. Maps of amplitude of low frequency fluctuations (ALFF) and regional homogeneity (ReHo) were estimated from six minutes of task-free functional data from a blood oxygen level-dependent (BOLD-weighted) 2D EPI sequence with the following settings: $T_R = 3000$ ms; $T_E = 32$ ms; FoV = 192×192 mm; matrix size = 64×64 ; number of slices = 46; slice thickness = 3 mm; inter-slice gap = 0 mm; resolution = 3 mm isotropic; 124 volumes. Subjects were instructed to stay awake, keep their eyes open and fixated on a displayed fixation cross, and remain still.

4.3 Image processing

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4.4 Estimation of intermodal coupling

For each subject, we calculated voxel-wise IMCo between CBF, ALFF, and ReHo modalities. Even though ALFF and ReHo are technically calculated from the same rfMRI modality, we refer to them as separate modalities because they measure different information.

First, we applied a grey matter mask to each of the three modalities. Then, within each masked modality, we globally scaled intensities to a mean of 0 and a variance of 1. This scaling is necessary because eigendecomposition is later performed on local covariance matrices, so if modalities are defined on drastically different scales, decomposition outputs will reflect differences in baseline overall variance between modalities rather than local covariance structures. Next, for each voxel, we extracted local neighborhoods from each of the three modalities and weighted voxels within these local neighborhoods proportional to a Gaussian kernel over their Euclidean distances from the central voxel - in our study, we used FWHM = 3 which corresponds to 7x7x7 voxel (14x14x14 mm) local neighborhoods and a standard deviation of 1.62 mm for the Gaussian kernel. Then, we calculated the 3x3 weighted covariance matrix between the neighborhoods, performed eigendecomposition on them, and extracted the proportion of variance explained by the first eigenvalue. Once all voxel-wise proportional first eigenvalues were extracted, we scaled these values such that the minimum was 0 and maximum was 1 and then performed a logit transformation so extreme values of coupling would be emphasized. This resulted in our voxel-level coupling value, where a large value means that voxel’s local covariance matrix could be well-summarized in a single dimension.

For reference, in the three-modality setting, coupling values of -2, 0, and 2 correspond to the first eigenvector explaining 41%, 67%, and 92% of the total variance in that local neighborhood, respectively. In the two-modality setting, coupling values of -2, 0, and 2 correspond to the first eigenvector explaining 56%, 75%, and 94% of the total variance in that local neighborhood, respectively.

4.5 Voxel-wise statistical analysis

We created descriptive coupling maps by taking the means and variances across all 803 subjects at each voxel location in volumetric space. We then projected these mean and variance maps to the FreeSurfer sphere using PySurfer for visualization of spatial heterogeneity and cortical patterns [TOCITE].

To investigate biological relevance of PCA-based IMCo, we used linear regression at each voxel to explore whether coupling was associated with age or sex effects. In all linear regressions, we controlled intra-scanner motion for both ASL and rfMRI scans. To control for multiple comparisons in these voxel-level tests, we controlled the false discovery rate at 5%

(?). Then, we created binary thresholded masks indicating which tests remained significant post-correction for both age and sex. For this and following analyses, we performed identical modeling of each of the three modalities individually to explore whether the presence of age and sex effects on modality intensities corresponded to the presence of age and sex effects on coupling values (Supplementary Materials).

To visualize the extent of voxels where coupling was associated with age and sex, we counted the proportion of voxels with statistically significant age or sex effects in each of the Yeo 7 functional networks as well as in Automated Anatomical Labeling (AAL) atlas subcortical regions of interest (??). We also projected the thresholded p-value maps to the FreeSurfer sphere for visualization and further analyses.

4.6 Spin testing

For each of the age and sex thresholded p-value maps projected to the FreeSurfer sphere, we then tested whether the proportion of significant voxels in each functional network was enriched when compared to the proportion of significant voxels overall. Because there is an underlying spatial distribution of significant voxels, we used the spin test (?). Briefly, the spin test is a conservative, permutation-based test that rotates the FreeSurfer sphere randomly to create an underlying null distribution that preserves spatial patterns. In our study, we estimated the null distribution over 2,000 permutations - for each permutation, we recorded the Jaccard similarity index between the thresholded p-value map and each of the Yeo 7 networks. Finally, for each network, we calculated the p-value as the proportion of null Jaccard similarity indices equal to or greater than the observed Jaccard similarity index.

4.7 Code availability

An R package for calculating PCA-based IMCo images is available at: https://github.com/hufengling/IMCo_PCA. All code for analysis is available at: https://github.com/hufengling/IMCo_analyses.

5 Results

5.1 Cortical coupling voxel-wise descriptive maps

We calculated voxel-wise mean and variance maps of coupling values to characterize spatial patterns in CBF-ALFF-ReHo coupling and visualized these on the FreeSurfer sphere. Throughout the cortical surface, all voxels showed strong coupling, and voxels with stronger average coupling also had higher variance between subjects. The average voxel-wise mean coupling value was 0.99 (sd = 0.37; range from 0.27 to 3.30). The average voxel-wise variance was 0.91 (sd = 0.20; range from 0.45 to 2.64).