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Title:

Voxel-wise Intermodal Coupling Analyses of Multiple Images Using Local Covariance Decompositions

Introduction:

There is increased availability of multi-modal scans for individual subjects, with each modality containing specific information about brain structure or function. While analysis of each modality independently is widely conducted, previous studies have shown the additional information in the local covariance structures between modalities, or intermodal coupling (IMCo), is often complementary and may unveil otherwise undetectable findings.[1–3] For example, in neurodevelopment, IMCo between cortical thickness and sulcal depth has been shown to change with age and vary between males and females.[2] IMCo of cerebral blood flow (CBF) and amplitude of low frequency fluctuation (ALFF) also showed changes based on age and sex.[1]

However, available IMCo methods are based on regression which is inherently asymmetric – that is, coupling depends on the order modalities are listed – and only defined for two modalities. Here, we propose a PCA-based improvement of IMCo which uses local covariance decompositions to define a symmetric voxel-wise coupling coefficient valid for any number of modalities. We further show this coupling coefficient is sensitive to biological effects for three modalities.

Methods:

Our study included 803 youths (340 males) from ages 8-23 (mean = 15.6; sd = 3.3) in the Philadelphia Neurodevelopmental Cohort [4] who completed T1-weighted MRI, arterial spin labeling MRI (ASL), and resting-state fMRI (rfMRI) of acceptable image quality. ASL and rfMRI scans were registered to T1 scans and pre-processed as previously detailed. We used ASL scans to calculate CBF, correcting for partial volume effects with BASIL.[5] We used rfMRI scans to calculate ALFF and regional homogeneity (ReHo). ALFF and ReHo were considered different modalities in the sense that they contain unique information.

For each subject, we calculated voxel-wise IMCo between three modalities – CBF, ALFF, and ReHo – by first applying a gray matter mask to each. Next, we scaled intensities within each modality to a mean of 0 and variance of 1. For each voxel, we extracted a local neighborhood from each modality and calculated the 3x3 weighted covariance matrix between the neighborhoods. Finally, we performed eigendecomposition on each weighted covariance matrix, extracted the first eigenvalue, scaled it to range from 0 to 1, and performed logit transformation. This coupling value represents how strongly modalities covary at each voxel.

We analyzed subject-level coupling maps using linear regression for age and sex effects, while controlling for in-scanner motion. We corrected for voxel-level multiple comparisons using the false discovery rate (Q < 0.05). Additionally, we explored whether age and sex effects were highly enriched in certain functional networks using the spin test.[6]



Results:

We observed strong CBF-ALFF-REHO coupling in cortical networks (Fig. 1) and subcortical regions. In the cortex, the association between coupling and age was enriched in frontoparietal (p = 0.0125) and default networks (p = 0.039), and the association between coupling and sex was enriched in the frontoparietal network (p = 0.0115) (Fig. 2). In subcortical structures, a high proportion of the caudate, pallidum, putamen, thalamus, and hippocampus showed associations between coupling and age (corrected p < 0.05), and a high proportion of the thalamus and hippocampus showed associations between coupling and sex (corrected p < 0.05).

Conclusions:

PCA-based IMCo offers a generalized approach for coupling of two modalities and a novel methodology for coupling of more than two modalities. We found local intermodal patterns of blood flow, resting state activation, and connectivity that evolve through neurodevelopment in frontoparietal and default networks. These findings are unique from those in individual modalities. As multimodal data become more available, PCA-based IMCo can serve as an additional descriptive and data reduction tool to allow for efficient analysis to uncover intermodal patterns of association.

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