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Title:

Voxel-wise Intermodal Coupling Analyses of K>=3 Modalities 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 but important findings.

In neurodevelopment, IMCo between cortical thickness and sulcal depth has been shown to be spatially heterogeneous, change with age, and vary between males and females.[1] IMCo of cerebral blood flow and amplitude of low frequency fluctuation also showed changes based on age and sex.[2] In multiple sclerosis lesion detection, inclusion of volumetric IMCo maps of T1, T2, PD, and FLAIR scans in each ordered pairwise combination led to improved sensitivity and specificity of the MIMoSA method over other popular automatic segmentation approaches.[3]

However, currently available IMCo methods are based on regression which is inherently asymmetric – that is, coupling depends on the order in which modalities are listed – and are 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 biologic effects for three modalities.

Methods:

Our study included 803 youth (340 males) in the Philadelphia Neurodevelopmental Cohort [4] with no history of psychoactive medication or medical disorders that could impact brain function who underwent T1-weighted MRI, arterial spin labeling MRI (ASL), and resting-state fMRI (r-fMRI) of acceptable image quality. ASL and r-fMRI scans were registered to T1 scans and pre-processed as previously detailed. We used ASL scans to calculate cerebral blood flow (CBF), with partial volume effects corrected for using BASIL.[5] We used r-fMRI scans to calculate amplitude of low-frequency oscillations (ALFF) and regional homogeneity (ReHo).

For each subject, we calculated voxel-wise IMCo between these three modalities – CBF, ALFF, and ReHo – by first applying a grey matter mask to each. Then, we globally scaled intensities within each modality to a mean of 0 and variance of 1. Next, for each voxel, we extracted a local neighborhood from each modality and and calculated the weighted covariance matrix between the three neighborhoods. Finally, we performed eigendecomposition on each weighted covariance matrix, extracted the first eigenvalue, scaled it to range from 0 to 1, and performed a 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 correcting for race and in-scanner motion. Additionally, we explored whether age and sex effects were more highly enriched in certain functional networks using the spin test.[6] We corrected for multiple comparisons using a false discovery rate of 0.05.



Results:

We observed strong CBF-ALFF-REHO coupling in cortical networks and subcortical regions. In the cortex, coupling varied with age in frontoparietal and default networks, while coupling did not vary strongly between males and females. In subcortical structures, coupling varied with age in the caudate, pallidum, putamen, thalamus, and hippocampus, while coupling varied with sex in only the thalamus and hippocampus.

Conclusions:

PCA-based IMCo offers a generalized approach for studying coupling of two modalities and a novel methodology for studying coupling of more than two modalities. In the context of CBF, ALFF, and REHO, three-modality coupling reveals age and sex changes in brain regions known to change over the course of neurodevelopment. These age and sex changes are unique from those in each individual scan. As multi-modality data become increasingly available, PCA-based IMCo can serve as an additional descriptive and data reduction tool to allow for more efficient analysis that uncovers intermodal patterns of association.

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