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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 but important findings. For example, 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] 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 youths (340 males) in the Philadelphia Neurodevelopmental Cohort [3] 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 cerebral blood flow (CBF), with partial volume effects corrected for using BASIL.[4] We used rfMRI 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. Next, we globally 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 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.[5] We corrected for voxel-level multiple comparisons using the false discovery rate (Q < 0.05).



**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 = 0.013) and default networks (p = 0.028), and the association between coupling and sex was enriched in the frontoparietal network (p = 0.009) (Fig. 2). In subcortical structures, a high proportion of the caudate, pallidum, putamen, thalamus, and hippocampus showed associations between coupling and age (q < 0.05), and a high proportion of the thalamus and hippocampus showed associations between coupling and sex (q < 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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