Multimodal Fusion of Brain Imaging Data: A Key to Finding the Missing Link(s) in Complex Mental Illness

Supplemental Information

Supplemental Material (a Summary of Multivariate Data-Fusion Approaches)

In this supplement, we provide a brief summary of several multivariate approaches as shown in Figure 5 and Figure 6 as initially described in an earlier review (1).

Joint ICA

Joint ICA (jICA) is a second-level fMRI analysis method that assumes two or more features (modalities) share the same mixing matrix and maximizes the independence among joint components (2). Joint ICA has been used on many combinations of modalities including ERP, MEG, fMRI, sMRI and dMRI (3-7). **Figure S1** shows results from fMRI and sMRI data analyzed using the jICA approach (5). The main finding was that group differences in bilateral parietal and frontal as well as posterior temporal regions in gray matter distinguished schizophrenia patients from healthy controls. Interestingly, patients showed a decrease of the link between gray matter linked and hemodynamic activity in temporal lobe regions. In a similar analysis of multitask data, results showed that schizophrenia patients showed more similar patterns of activity than the controls, suggesting their brains are less uniquely activating when performing very different tasks (8).

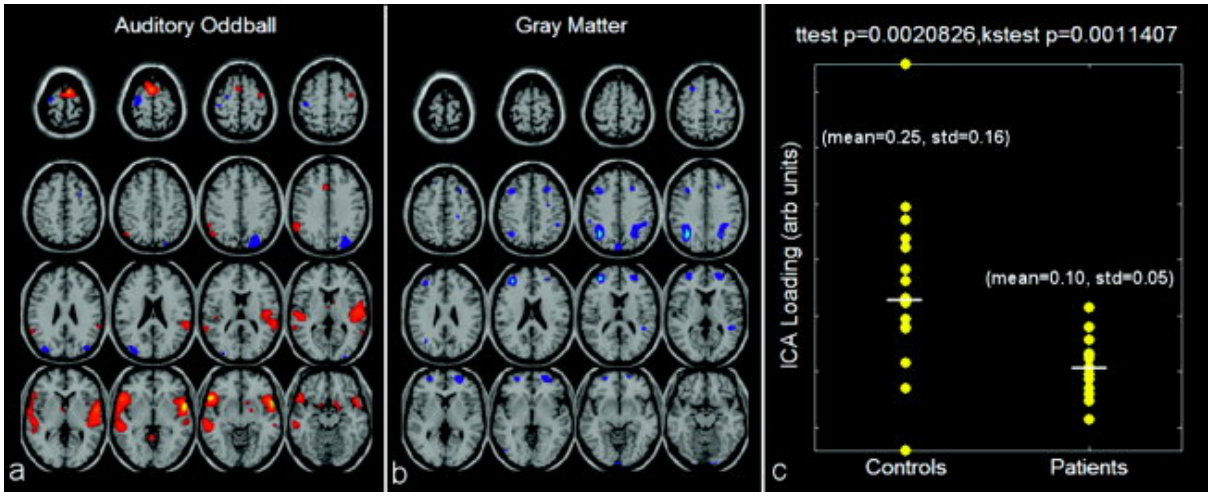

Figure S1. Auditory oddball/gray matter jICA analysis. Only one joint component demonstrated a significant difference between patients and controls. Source maps for the auditory oddball fMRI data (left) and gray matter (middle) data are presented along with the loading parameters for patients and controls (far right). Reproduced with permission from Calhoun *et al.* (5).

Multimodal CCA

Multimodal CCA is used to identify a coordinate system that maximizes inter-subject covariations among two data sets (9), with a different mixing matrix for each modality. This method decomposes each dataset into a set of canonical variants (CVs) (i.e., mixing profile along subjects) and their corresponding spatial components. The CVs capture the contribution or weights of each modality for all subjects and are linked if they modulate similarly across subjects. Compared to jICA which assumes multiple data sets to have the same mixing matrix, mCCA is flexible in that it allows both strongly and weakly correlated links between two features, as shown in Figure 7. However the associated source maps may can be harder to interpret, especially when the canonical correlation coefficients are not sufficiently distinct (10). Multimodal CCA is capable of jointly analyzing very diverse types of data and can also be extended to multi-set CCA so as to work on more than two modalities (11).

Partial Least Squares

Partial least squares is another constituent in the family of multivariate data analyses, which is based on a linear relationship defined between a dependent variable and predictor variables. The goal of PLS is to determine which aspect of a set of observations (e.g., imaging data) are directly related to another set of data (e.g., cognitive scores, experimental design, etc.) (12). PLS was first applied to multimodal fusion in the context of multiway PLS (N-PLS) (13), in order to find associations between fMRI time courses (dependent variables) and the EEG spectral components (independent variables) for one participant. Subsequently, multimodal PLS (MMPLS) (14) was proposed to characterize the linked patterns between sMRI and PET. Multimodal PLS can be performed in either blind or semi-blind (informed PLS) manner. Note that PLS is similar to CCA in that they both maximize between-set correlations, however, PLS needs additional definition of dependence and works best when this dependence is explicitly assessed (15) among the constituents of the datasets; by contrast, CCA does not assign predictive/dependent labels and treats both modalities equally (16). PLS tends to be a useful tool to examine interactions between human behavior/cognition or experimental design and related brain measures (17), although interpretational difficulties can manifest when the connected effects do not correspond to a priori expectations.

mCCA+jICA

Previous studies which combined brain structure and function (18,19) support the concept of inter-subject correlation between multimodal mixing profiles. As a blind data-driven model (20,21), mCCA+jICA balances the case of unique and common information among modalities as well as spatial independence. It takes advantages of two complementary methods: mCCA and jICA, thus enables the identification of both strong and weak inter-modality links. In particular, mCCA provides an initial ordering of linked components via

correlation which are then further decomposed by jICA. The mCCA+jICA approach has been extended to handle more than two modalities by replacing the multimodal CCA with multi-set CCA (11), allowing robust identification of the correspondence among multiple diverse data types. In sum, mCCA+jICA enables investigation of the vital question of whether certain disease risk factors are shared or are distinct across multiple modalities. **Figure S2** presents an example of the application of this approach to fMRI-sMRI–dMRI fusion in a schizophrenia study (1,22).

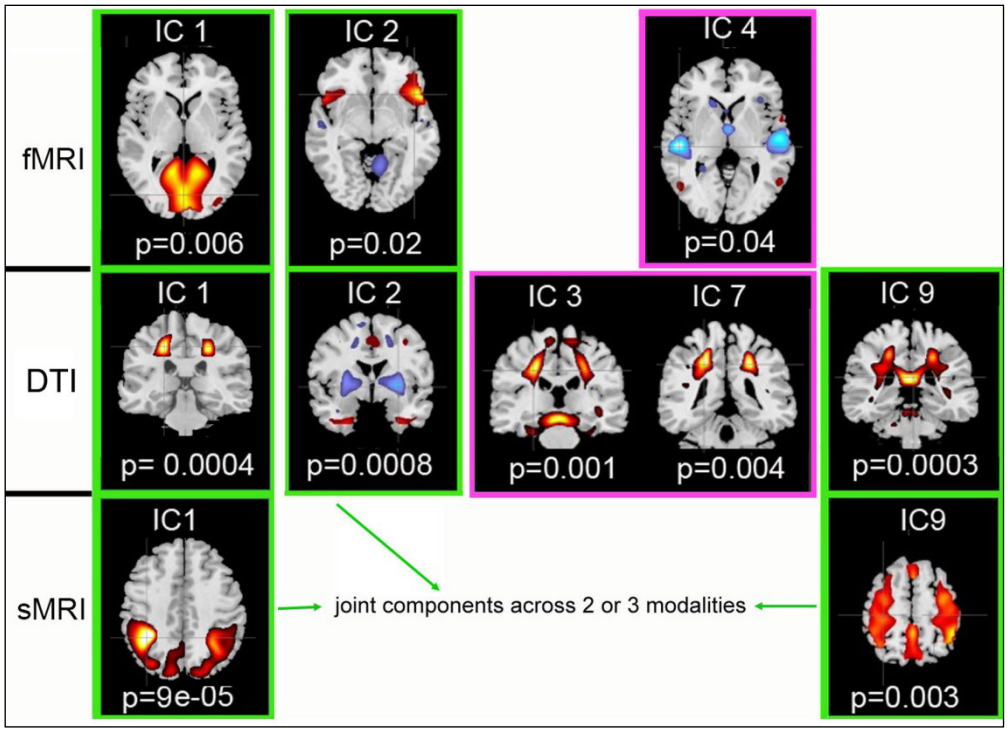

Figure S2. MCCA+jICA enables people to capture components of interest that are either common or distinct across modalities. For example, when examining group differences across 3 modalities, joint ICs are significantly group-discriminative in more than 2 modalities (green framed), while modality-specific discriminative ICs (pink framed), i.e., fMRI_IC4, DTI_IC3 and DTI_IC7 only show significant group difference in a single modality. Reproduced with permission from Sui *et al.* (23).

Linked ICA

Linked ICA is a probabilistic approach based on a modular Bayesian framework, which is designed for discovering common characteristics across multiple data sets (24). The

combined features can potentially have different noise levels, units and intensity distributions, each of which is decomposed by a Bayesian tensor ICA model (25). Linked ICA can detect and isolate single-modality noise and has been used to study autism patients by combining FA, GM and resting state fMRI connectivity (26). However, it is much more computational demanding, and the spatial maps of the decomposed components tend to be scattered and harder to interpret.

Parallel ICA

Liu *et al.* first proposed parallel ICA (27) to investigate significant correlations between brain dysfunctional regions and putative disease susceptible single nucleotide polymorphisms (SNPs), providing a tool that associates genomic SNP factors with phenotypic imaging findings in a multivariate format. Parallel ICA effectively relaxes the assumption of one mixing matrix and estimates a separate, but linked, mixing matrix for each modality. This method can also be used to investigate fMRI-EEG associations or other multi-modal associations. Vergara *et al.* extended it to three-way fusion by analyzing links among genetics (28), brain structure and brain function. Chen *et al.* further incorporated single or multiple genetic references into the model, called pICA-R, to guide the exploration of genomic risk for gray matter abnormalities in schizophrenia (29,30), which may serve as a useful approach in imaging genomics to discover reliable genetic risk factors under a scenario of relatively high dimensionality and small effect size. A full review of parallel ICA in the context of imaging genetics studies can be found in Pearlson *et al.* (31).

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