Multimodal Fusion of Functional and Structural Data to Recognize Longitudinal Change Patterns in the Adolescent Brain

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***Abstract*—Functional and structural magnetic resonance imaging (fMRI/sMRI) are extensively used modalities for studying brain development. While individual modalities may overlook crucial aspects of brain analysis, combining multiple modalities allows us to leverage the benefits of revealing hidden brain connections. To analyze multivariate change patterns in brain function and structure with increasing age across the entire brain, we employ a symmetric multimodal fusion approach that combines multiset canonical correlation analysis and joint independent component analysis. In this study, we present a novel approach to analyze linked longitudinal change patterns in functional network connectivity (FNC) and gray matter (GM) data derived from the large-scale Adolescent Brain and Cognitive Development dataset. Our approach uncovers significant pattern changes in both modalities. Specifically, we identify highly structured functional change patterns and structural change patterns that include increased brain functional connectivity between the visual and sensorimotor domains in the fMRI data, as well as changes in the bilateral sensorimotor cortex in the sMRI data. Overall, our study demonstrates the strength of our approach in uncovering longitudinal changes in FNC and GM, provides valuable insights into the dynamic nature of brain connectivity and structure during adolescence, and sheds light on potential gender-related differences in these processes.**

***Index Terms*—Delta FNC, Longitudinal study, mCCA+jICA, MRI, Gray matter**

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I. INTRODUCTION

Magnetic resonance imaging (MRI) is a widely utilized method for acquiring valuable brain information and one of the only modalities that can visualize brain structure and function. Structural neuroimaging modalities, such as structural MRI (sMRI) and diffusion MRI (dMRI), provide insights into the anatomical structure and tissue composition of the brain. In contrast, functional neuroimaging modalities, such as fMRI based on blood-oxygenation-level-dependent (BOLD) signal, indirectly measure brain function and activity [1], [2]. Previous studies have predominantly examined functional and structural measures independently when analyzing the brain. However, there has been a rapid increase in the utilization of combined structural and functional MRI data [3]. Multimodal fusion of neuroimaging data is a technique that integrates data acquired from multiple imaging modalities and techniques. This approach aims to overcome the inherent limitations of individual modalities and gain a deeper understanding of brain dynamics [4]–[6]. The primary objective of multimodal fusion is to enhance the analytical power of each modality through joint analysis, rather than separate analyses of each modality.

In order to analyze the shared information among the features found in different imaging modalities, we used multiset canonical correlation analysis + joint independent component analysis (mCCA+jICA) method, a widely recognized and extensively used multimodal fusion approach [7]. mCCA+jICA, is a data-driven multivariate fusion technique [8], [9] that simultaneously analyzes multimodal data by combining mCCA and jICA in a two-step process [4]. In the first step, mCCA is utilized to identify highly correlated components between multiple modalities [7], [10]. This is followed by the application of jICA in the second step to decompose these correlated components into spatially independent components, known as ICs. The mCCA+jICA algorithm has been employed [7] to combine fMRI contrast maps and diffusion tensor imaging (DTI) fractional anisotropy (FA) maps for examining group differences among healthy controls (HCs), schizophrenia patients (SPs), and bipolar patients (BPs). Importantly, that study found that the combined algorithm yielded increased accuracy in group classification compared to using the constituent algorithms individually. Ouyang et al. have used the mCCA+jICA approach to identify patterns of gray matter (GM) and white matter (WM) covariance in patients with Alzheimer's disease [11]. Similarly, Kim et al. utilized mCCA+jICA with multimodal sMRI and DTI data from patients with obsessive-compulsive disorder and HCs, revealing significant alterations in the interconnected networks of GM and WM [12]. But, to the best of our knowledge, no previous studies have been conducted to estimate the changes in sex-related multivariate patterns coupling in FNC and GM associated with age progression using the mCCA+jICA multimodal fusion analysis method.

In this study, we propose a novel approach to investigate the relationship between within subject age-related changes in whole-brain structure and function at an individual level. For each participant, we calculate cell-wise differences (ΔFNC and ΔGM) and then estimate covarying multivariate patterns (functional change patterns (FCPs) and structural change patterns (SCPs)) using the mCCA+jICA multimodal fusion method. By performing a one-sample t-test on the loading parameters of the resulting multimodal components, we identify several FCPs and SCPs that exhibit significant longitudinal differences. Furthermore, we explore the interaction between functional and structural changes in both males and females. The rest of this paper is structured as follows: the method section describes the data preprocessing steps, workflow, and analysis procedures. In the results section, we present the findings related to functional and anatomical brain changes associated with age. Lastly, we discuss the significant implications of our findings in the conclusion section.

II. Materials and Methods

A. Adolescent Brain Cognitive(ABCD) Data Summary

In this investigation, the dataset from the Adolescent Brain Cognitive Development (ABCD) (https://abcdstudy.org/) study, which was conducted to monitor the changes occurring in the human brain as individuals transition from childhood to adolescence, has been utilized. The ABCD project involved more than 11,800 children, aged 9 to 10 at the baseline session, who had multiple MRI scans, and their health and demographic information was collected as well. The ABCD dataset is accessible through the National Institute of Mental Health Data Archive (NDA) website (https://nda.nih.gov/). The NDA gathers data from various research endeavors across diverse scientific disciplines and shares the ABCD data as an open-source dataset, fostering collaborative research and exploration. To ensure data quality, the fMRI data was preprocessed using a robust independent component analysis (ICA)-based framework known as Neuromark. This framework compares data across subjects to identify brain networks while accommodating individual variations within the networks [13]. In this study, a subset of 2,734 participants with both baseline and two-year follow-up scanned data for both functional network connectivity (FNC) and gray matter volume was selected.

B. Preprocessing of fMRI Data and Functional Feature Extraction

The data preprocessing steps involved a combination of the FMRIB Software Library v6.0 (FSL) toolbox and the Statistical Parametric Mapping 12 (SPM) toolbox in MATLAB 2020b. To correct for subject head motion, the FSL MCFLIRT tool was employed to perform rigid body motion correction. Following the motion correction, the distortion in the fMRI images was addressed using field map files. These field maps were obtained by capturing volumes with phase encoding in the anterior-posterior (AP) and posterior-anterior (PA) directions using the FSL tool topup. By utilizing the output field map coefficients obtained from the FSL tool applytopup, the distortion in the fMRI volume was corrected. Subsequently, the fMRI data were smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm and warped to the standard Montreal Neurological Institute (MNI) space with a spatial resolution of $3 \times 3 \times 3$.

After preprocessing, we utilized a fully automated spatially constrained ICA technique to extract intrinsic connectivity networks (ICNs) and their corresponding time courses (TCS) from the ABCD dataset. The extraction was performed using the Neuromark_fMRI_1.0 template [13]. This template was created by calculating replicated networks from two datasets of HCs: the Human Connectome Project (HCP) dataset, consisting of 823 selected individuals, and the Genomics Super Struct Project (GSP) dataset, consisting of 1005 selected subjects. Detailed information about the Neuromark template can be obtained from the website http://trendscenter.org/data and in the GIFT toolbox. Importantly, the chosen spatial priors have been demonstrated to exhibit high reliability across different pipelines, datasets involving both adults and adolescents, and various populations [14].

C. Preprocessing of sMRI Data

sMRI data was preprocessed using the statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/), software which was executed in the MATLAB 2020b environment. Initially, the structural images were subjected to segmentation to separate the gray matter, white matter, and cerebrospinal fluid (CSF), while also considering modulation by the Jacobian. This process resulted in voxel-wise maps of gray matter volume (GMV). Subsequently, the GMV maps were smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm, enhancing the spatial smoothness of the data.

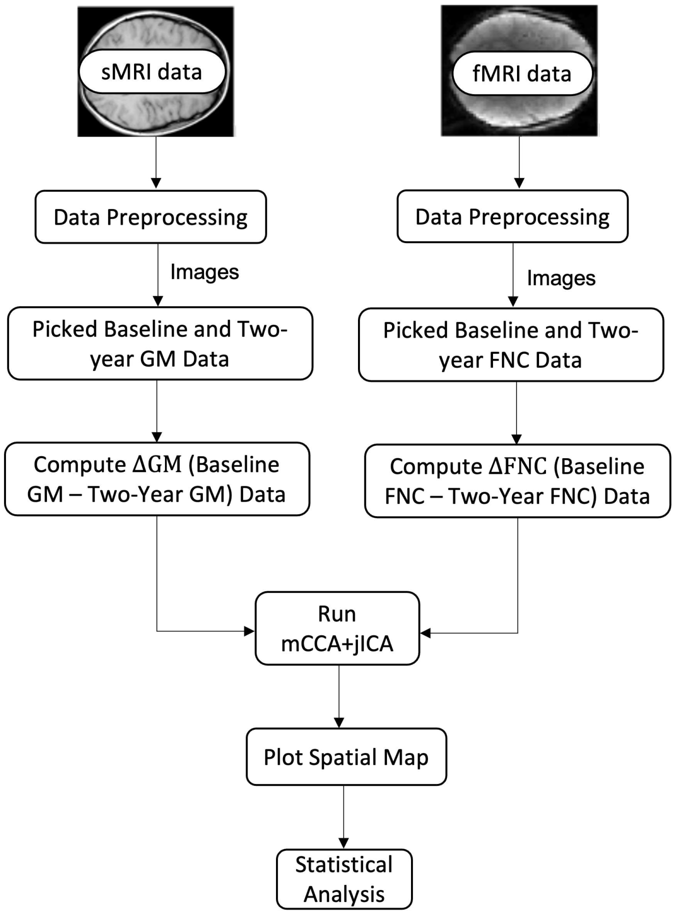


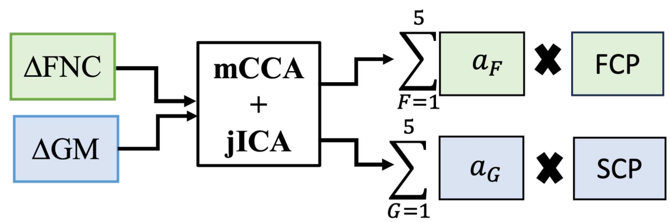
Fig. 1. Block diagram of the functional and structural change patterns recognition workflow .

D. Models

In our investigation, we utilized the subject-specific fMRI and sMRI data from both the baseline and two-year scans. To characterize changes in functional network connectivity (FNC) and gray matter (GM), we computed the cell-wise differences between the baseline and two-year data. These difference matrices, denoted as ΔFNC and ΔGM, represented the changes in FNC and GM over time, respectively. Next, we applied the mCCA+jICA method to deconstruct the ΔFNC and ΔGM matrices. This approach allowed us to capture co-varying patterns of change, namely functional change patterns (FCPs) and structural change patterns (SCPs), respectively. We estimated five components for both GM and FNC data, where this optimal number of components were estimated using the elbow criteria. The mCCA+jICA model equation used in our experiment is expressed as follows:

$$X_k = A_k \cdot S_k \tag{1}$$

In this equation, the dimensionality of the data matrix X is 2734 (subjects) × cells (for fMRI, the upper triangular elements of the ΔFNC matrix; for sMRI, the number of voxels). The dimensions of A are 2734 × 5 (components), S is 5 (components) × cells, and k = 2 is the number of modalities. This effectively models the input data as following :



Here, ΔFNC represents the difference between the baseline (F_0) and two-year (F_2) functional network connectivity (FNC) data, while ΔGM corresponds to the difference between the baseline (G_0) and two-year (G_2) gray matter (GM) data. The FCPs and SCPs source matrices capture the most independent patterns of functional and structural changes, respectively. The terms a_F and a_G refer to the subject-specific loading parameters for each component in the FNC and GM data, respectively. These loading parameters quantify the contribution of each subject to the respective components.

After performing the mCCA+jICA estimation, we proceeded to assess the loading parameters and source matrix. To identify FCPs and SCPs exhibiting significant longitudinal changes compared to zero, we conducted one-sample t-tests on the loading parameters a_F and a_G of both modalities. The statistical significance was evaluated at a 95% confidence level, adjusted for multiple comparisons. Furthermore, we separated the male and female loadings of GM and FNC data. We calculated the correlation between the GM and FNC loadings, specifically between GM male loadings and FNC male loadings, as well as between GM female loadings and FNC female loadings. By calculating the difference between these correlations (female - male), we evaluated the strength of coupling between GM and FNC loadings in relation to gender. A significant positive difference suggests that the coupling between GM and FNC loadings is stronger in females compared to males.

III. Results

The Neuromark template included a total of 53 replicable networks, which were categorized into 7 domains based on their anatomical and functional characteristics. These domains include subcortical, auditory, sensorimotor, visual, cognitive control, default mode, and cerebellar domains [14]. We present our experimental outcomes in Fig 2, which consists of spatial maps illustrating the connections between multivariate FCPs and SCPs. The figure displays 5 components of FCPs along

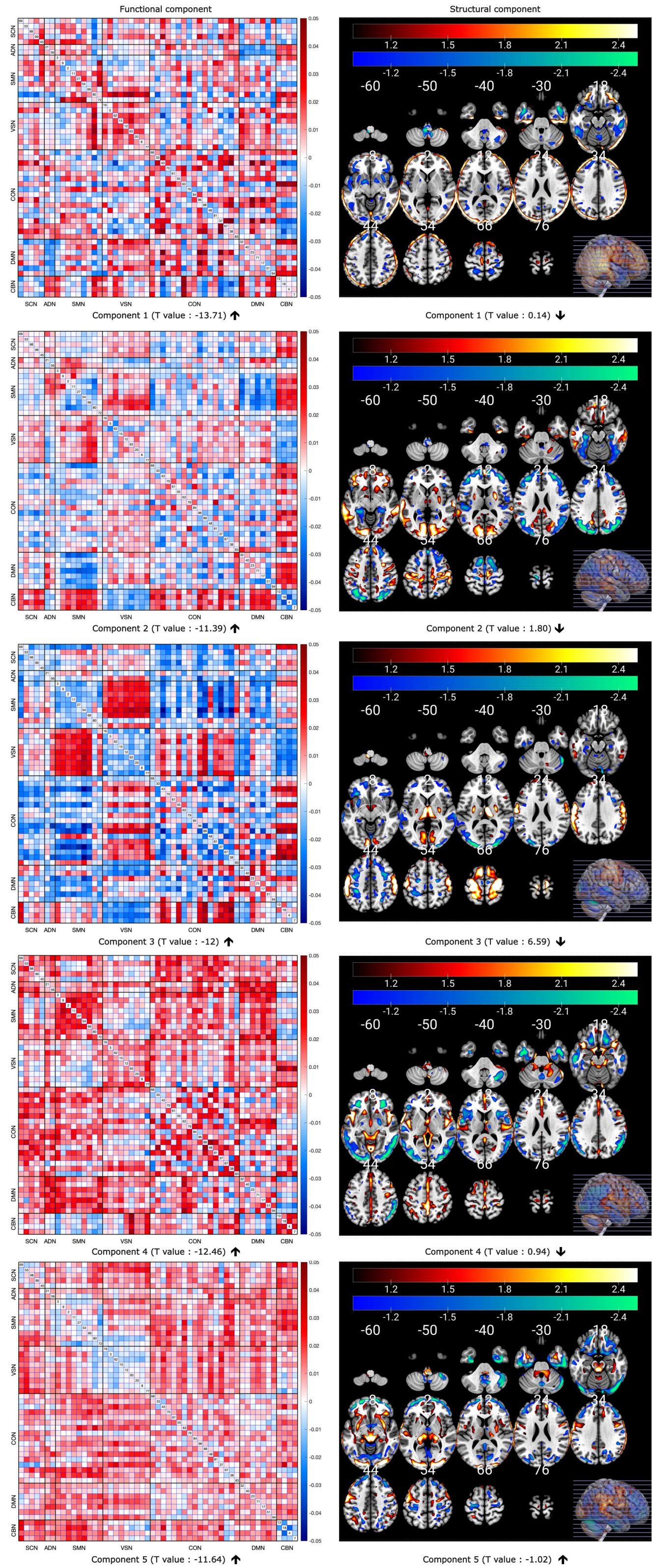


Fig. 2. FNC components and spatial map of GM components. Here, Component 3 from both functional and structural data exhibits highly structured changed patterns.

with corresponding spatial maps of SCPs components, along with their associated T-values. A high negative (or positive) T-value indicates increased (or decreased) expression of the specific FCP with age [15]. Furthermore, the associations of FCPs and SCPs components with increased age are also depicted by the upper and lower arrow. Here the upper and lower arrow indicate the increasing and decreasing pattern changes with age respectively. The results reveal notable modularity, suggesting structured changes that occur over the two-year period.

The functional connectivity patterns (FCPs) associated with components 2 and 3 exhibit significant changes with increased age in the developing brain. Both components show an increasing trend with age, as indicated by their negative T-values. Component 3 demonstrates an increased brain functional connectivity between the visual domain (VS) and sensorimotor domain (SM) in the FNC data. Correspondingly, there are decreasing changes in the bilateral sensorimotor cortex in the sMRI data over the two-year period. Furthermore, the FCP of component 3 reveals a decreasing trend with age in the functional connectivity between the VS and cerebellar domain (CB), as well as between the SM and cognitive control domain (CO).

After applying the multimodal fusion technique, we calculated the Pearson correlation between the loading parameters across all FCPs and SCPs (separately for males and females). The aim was to investigate the gender differences in coupling (subject expression-level associations). Our analysis revealed that females showed stronger coupling between SCP component 2 and FCP component 1 (Δr = 0.128, FDR-corrected, P = $2.1895e^{-11}$), FCP component 3 (Δr = 0.102, FDR-corrected, P = $1.0081e^{-07}$), and FCP component 4 (Δr = 0.111, FDR-corrected, P = $6.7136e^{-09}$) compared to males. This finding suggests that females who contribute the most to the structural change pattern (SCP component 2) also significantly contribute to the FCPs of components 1, 3, and 4. Based on the obtained correlation values, we can conclude that females exhibit a stronger coupling between the FCPs and SCPs expressions compared to males. Additionally, we conducted a two-sample t-test based on gender information using the loading parameters of both modalities. Our analysis revealed that males exhibit smaller change pattern expression in SCP for component 2 compared to females.

IV. Discussion and Conclusions

This paper presents a novel approach to examine the relationship between multivariate brain functional and structural change patterns using FNC matrices and GM data. The primary objectives of this study are to investigate whole-brain structural and functional changes over a two-year period, explore age-related trends in these changes, and analyze the coupling between structural and functional changes based on gender. The analysis utilizes functional and GM data from the ABCD dataset. The results reveal significant changes in several FCPs and SCPs over the two-year period. Furthermore, the study identifies that females exhibit stronger coupling between functional change patterns (components 1, 3, and 4) and structural change patterns (component 2) compared to males. These findings emphasize the potential of the proposed approach as a valuable tool for evaluating whole-brain functional and structural changes and their coupling in longitudinal studies involving both males and females.

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