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Functionally-Adaptive Gray and White Matter Structural Basis Sets via Dynamic Fusion of Multimodal MRI Data

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***Abstract*—The exact nature of the coupling of brain structure and function has long been an open area of research. Often, this question is approached by first defining a single structural basis set, and then estimating functional brain activation time courses as a linear combination of these structural bases. However, knowing that functional brain activity and connectivity vary over time, so might the nature of these structural/functional couplings. Thus, a single rigidly defined, "functionally unaware" structural manifold may be insufficient to describe structure/function linkages across a whole functional time series. Here, we introduce dynamic fusion, an ICA-based symmetric fusion, and show evidence that challenges current approaches and suggests time-resolved structural basis sets can better represent changing functional manifolds. We perform dynamic fusion using measures of both gray matter (GM) and white matter (WM) structure and present results that may indicate a stronger link between WM structure and dynamic brain function than in GM.**

Keywords—multimodal data fusion, dynamic FNC, fMRI, sMRI, DTI, dynamic fusion, structure-function coupling

I. Introduction

While neuroimaging has become a powerful non-invasive tool to study the human brain, each of the wide range of imaging modalities captures only a fraction of available brain information at a given moment and has a unique set of inherent limitations, resulting in a somewhat incomplete picture of the brain from a single modality alone. A class of approaches known as multimodal data fusion have been developed to overcome such limitations by enabling integration of complementary data across various neuroimaging modalities. The umbrella of multimodal data fusion spans a wide range of techniques to reveal hidden linkages between modalities, which can be broadly divided into two categories: symmetric and asymmetric. In asymmetric fusion, data from one modality is used to constrain the analysis from another modality, whereas in symmetric fusion each imaging modality contributes equally to the joint analysis, taking full advantage of the combined information across datasets [1], [2].

A prominent application of multimodal fusion in neuroimaging is to study the coupling of brain structure and function; however, this question comes with the common challenge of dimensional incongruence, i.e., fusing data from a structural "snapshot" of the brain with a functional "video" that contains the added time dimension. To solve this and achieve the correct dimensions for fusion, typically one must heavily summarize over the temporal dimension of the functional magnetic resonance imaging (fMRI) data by computing measures such as static functional network connectivity (FNC) or amplitude of low-frequency fluctuation (ALFF), effectively eliminating the rich temporal information all together [3], [4], [5]. Recent work has attempted to integrate time-resolved measures of FNC (e.g., dynamic FNC states) to structural brain maps via multimodal fusion, which has enabled deeper investigation of the relationship between functional dynamics and structural brain variation [6], [7]. Lately, another line of work has emerged for studying structure-function coupling via eigenmode decomposition of structural graphs (e.g., structural connectomes derived via diffusion imaging [8] or cortical surface geometry [9]) into a single basis set representing structural harmonics, then projecting the fMRI signal at each timepoint as edge weights onto the discovered structural manifold. The former represents a symmetric fusion approach, while the latter can be classified as asymmetric fusion (structural basis constrains analysis of functional data); however, both of these approaches for studying time-resolved structure-function coupling suffer from a certain rigidity, in that they do not allow flexible linkages between structure and function across time.

Here, we introduce our ICA-based symmetric fusion approach that allows for the identification of a temporally adaptive basis set that is inclusive of both structure and function, which we term "dynamic fusion". Here, we highlight three key results: 1) cross-fusion comparisons revealed a small set of "static" (i.e., relatively stable) structural components, as well as a large set of "dynamic" components, the dynamic fusion approach enabled flexible linkages between structure and time-evolving function, 2) dynamic components exhibit stronger schizophrenia (SZ) vs. control group differences than static components, suggesting the "functionally aware" dynamic components may capture clinically-relevant structure-functional linkages that are missed by standard approaches, and 3) WM components show evidence for stronger links to temporally-evolving functional data than GM components.

II. Data & Methods

A. Data Description

We analyzed functional and structural MRI data from the HCP [10] and FBIRN [11] datasets, as well as diffusion tensor imaging (DTI) from HCP. In both datasets, resting state fMRI (rs-fRMI) data were preprocessed with a standard pipeline that included brain extraction, slice-timing, and motion correction steps. Preprocessed data were then registered into structural MNI space, resampled to 3 mm^3 isotropic voxels, and spatially smoothed using a Gaussian kernel with a 6 mm full-width at half-maximum (FWHM) on a per-subject basis. Dynamic FNC analysis of rs-fMRI differed between the HCP and FBIRN datasets, and the pipelines are detailed below.

All structural MRI data were preprocessed using statistical parametric mapping (SPM12) under the MATLAB 2019 environment. Structural images were segmented into gray matter, white matter, and CSF using the modulated normalization algorithm, resulting in outputs as gray matter volume (GMV), which were subsequently smoothed using a Gaussian kernel with a FWHM = 6 mm. DTI data from HCP were processed using the FSL software package with a standard pipeline for motion and eddy current correction. Diffusion tensor models were fit on the corrected data to compute scalar fractional anisotropy (FA) maps, which were used as the structural inputs to the WM dynamic fusion experiments.

B. Time-resolved FNC in HCP

We utilized data from 833 subjects (390 male, avg. age = 28.7 years) from the HCP 1200 dataset [10]. Resting state fMRI (rs-fMRI) data were processed via spatially constrained ICA (scICA) using the NeuroMark_fMRI_1.0 template [12] in GIFT [13] to extract subject-level spatial maps for each of the 53 intrinsic connectivity networks (ICNs) in the template, as well as their respective activation time courses. Dynamic FNC (dFNC) was computed from ICN time courses using a sliding window Pearson correlation (SWPC) approach outlined in [14], with the exception that the window size used in our analysis was 20 TR (~15s; TR = 0.72s). K-means clustering revealed five dFNC states, and subject-average connectomes were computed for each state for dynamic fusion.

C. Time- and Frequency-resolved FNC in FBIRN

We utilized an age- and gender-matched dataset including 150 individuals with SZ (114 male, avg. age = 38.8 years) and 160 controls (HC; 115 male, avg. age = 37.0 years) [11]. Again, rs-fMRI were preprocessed via the NeuroMark pipeline, and time- and frequency-resolved functional network connectivity (FNC) patterns were then computed from the rsfMRI data using the filter-bank connectivity (FBC) approach [15]. Briefly, FBC utilizes a filter bank, i.e., an array of systems used to filter a time series into different frequency bands (typically non-overlapping and spanning the full frequency spectrum of the data), which enables estimation of FNC within a given frequency range. We designed our filter bank to contain 10 Chebyshev type-2 infinite impulse response filters that evenly cover the full frequency spectrum of the fMRI time series (0.00 – 0.25 Hz). K-means clustering identified six distinct states with unique connectivity signatures and spectral occupancy across frequency bands. In this work, we focus on three of the six states at the extremes of the frequency range: State 1 (low-frequency HC-dominant), State 2 (low-frequency SZ-dominant) and State 6 (high-frequency SZ-dominant) (Fig. 1). For more detail on the FBC approach and state clustering used here see [7], [15].

D. Dynamic Fusion

We used multi-set canonical correlation analysis + joint independent component analysis (mCCA + jICA) [16] to perform fusion of both static (GMV/FA maps) and temporally-resolved (SWPC/FBC states) neuroimaging features. The combined mCCA + jICA model is designed to allow for the identification of both strongly and weakly correlated joint components that are also independent from one another by employing mCCA in the first step to generate flexible linkages between the modalities and subsequently applying jICA on the associated maps in the second step. The mCCA + jICA framework is defined under the assumption that a multimodal dataset, X_k, is a linear mixture of m sources (S_k) mixed by non-singular matrices (A_k), here, k = (1,2). The effective mCCA + jICA framework can be defined as $X_k = (D_k W^{-1}) S_k$, where the modality-specific mixing matrices are defined as $A_k = D_k W^{-1}$. Further details can be found in [17], [18], [19].

Specifically, in the rs-fMRI experiments for both HCP and FBIRN, we performed separate data fusion experiments for each dFNC state (five and three, respectively): State 1↔GMV, State 2↔GMV, etc. This experimental design resulted in a set of structural (GMV or FA) components (model order = 10) optimized to each time-resolved state independently. Cross-fusion comparisons of these structural components across experiments revealed structural manifolds unique to each state (i.e., GMV/FA components related to frequency-specific functional connectivity dynamics), as well as some that were identified across multiple states, indicating a "static" structural component.

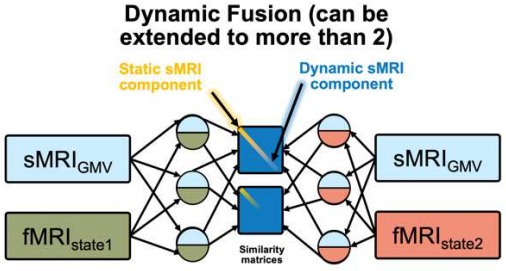

Fig. 1. Dynamic Fusion Example

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III. Results

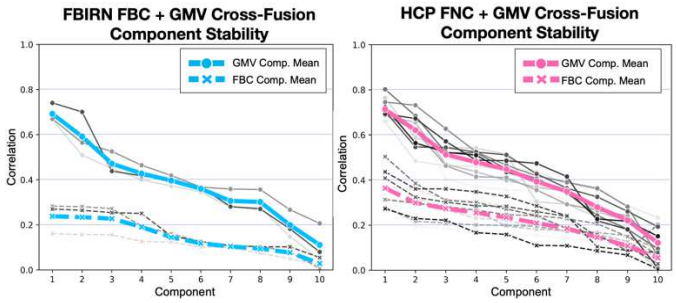

Fig. 2. Dynamic fusion in HCP and FBIRN datasets reveals a small set of static structural components and a larger set of functionally influenced "dynamic" components.

Fig. 2 illustrates the cross-fusion stability of GMV (solid lines) and FBC/FNC (dashed lines) component maps for both FBIRN (top) and HCP (bottom) experiments. We observed low correspondence overall for the functional components (dashed lines), which was expected as each of the dFNC states have unique connectivity signatures, and, in the case of the FBIRN data, are found in distinct frequency bands. Though the GMV components exhibited higher stability overall, we found fairly high cross-fusion correspondence in the first few components ($|r| > 0.55$) followed by a fairly steep drop-off of component correspondence, suggesting some of the structural components are functionally influenced (i.e., "dynamic"), while some are not (i.e., "static").

A. *Dynamic Components Exhibit Stronger Group Differences than Static Components*

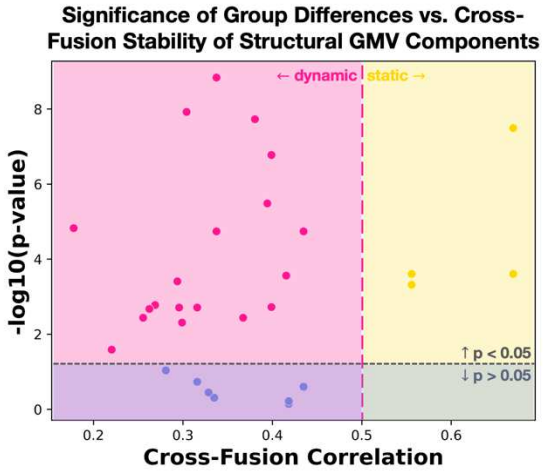

Fig 3. Dynamic components (max cross-fusion correlation < 0.5) show stronger group differences (-log10(p_{FDR})) in loading parameters than static components.

For each of the 30 components derived across the three FBIRN fusion experiments, we computed group differences (SZ vs. controls) between the GMV component loading parameters and defined each component as "static" or "dynamic" based on the max cross-fusion correlation > or < 0.5, respectively (Fig. 3). While all four static components exhibited significant group loading differences, most (19/26) dynamic components did as well. In fact, 8 of the dynamic components showed stronger group differences than 3 of the 4 static components. These results suggest dynamic GMV components may better represent clinically-relevant structure-function linkages than traditional fusion or structural dynamics approaches.

B. *White Matter Components Show Stronger Links to Temporally-Evolving FNC*

Of the total 833 HCP subjects, 737 had processed FA maps available, thus we replicated the HCP GMV dynamic fusion experiments in this subset of subjects. Results comparing the GMV and FA dynamic fusion experiments are shown in Fig 4. While the overarching relationship between structure and function holds in the FA data (higher stability in structural components than functional components), there are a few key differences to highlight. First, the FA experiment shows evidence for one highly static (mean cross-fusion correlation = 0.75), with a steep drop-off to the rest as dynamic components, as opposed to a gradual decrease in cross-fusion stability and 2-3 "static" component maps. Second, the overall cross-fusion stability of the components is lower in the FA experiments compared to GMV, which may suggest a stronger linkage to the changing functional manifolds in each distinct dFNC state fusion, thus leading to lowered cross-fusion stability. To assess this hypothesis, we compared the correlations between the structural and functional loading parameters for all components in the GMV and FA experiments, and found that the correlations were indeed higher in the FNC + FA components ($p = 0.0043$, $t = -2.927$).

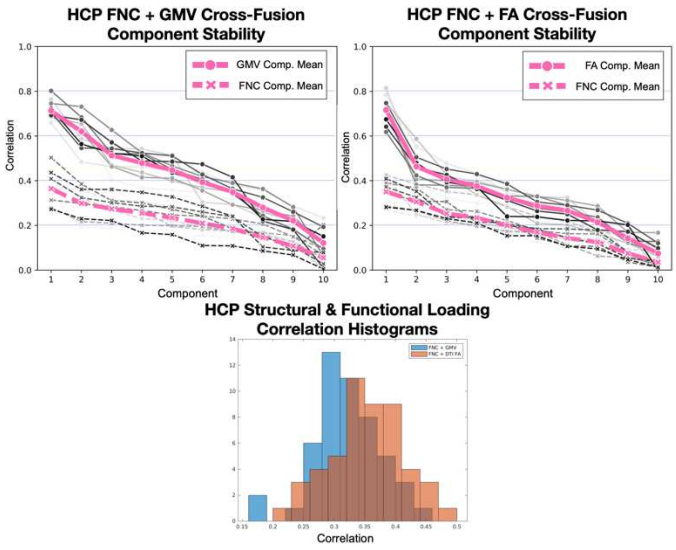

Fig. 4. White matter (FA) components show one highly stable component, with a steep drop-off to dynamic components that show overall lower cross-fusion stability than corresponding GMV components in the same subjects (top row). Higher correlation between structural and functional loading parameters was observed in FA fusion experiments compared to GMV fusion (bottom row; $p = 0.0043$, $t = -2.927$).

IV. Discussion

Here, we propose an approach for investigating dynamic/flexible linkages between brain structure and time-varying brain function, termed dynamic fusion. Our approach

is fully data driven and allows both modalities to contribute to the fusion equally (i.e., symmetric fusion), thus enforcing fewer assumptions and enabling a broader spectrum of flexibility than recent works in structural dynamics. We show that dynamic fusion identifies functionally-adaptive structural basis sets that are specific to each dFNC state and absent when static FNC is used as functional inputs, which challenges the notion that a single structural manifold is sufficient or appropriate for representing every time point in an rs-fMRI scan. Our results also suggest that dynamic components, which are driven by the changing linkage to varying functional manifolds, capture stronger SZ/control group differences than static components, indicating they may encode unique aspects of clinically-relevant pathophysiology that are missed with traditional fusion approaches. Finally, we show evidence that suggests dynamic fusion of white matter data (FA maps) shows stronger linkages to temporally-evolving functional data than corresponding gray matter data (GMV maps) in the same subjects. This finding, though preliminary, illustrates how dynamic fusion can be applied towards the investigation of open questions in the field of neuroscience that are currently the topics of much debate. Future work may focus on replicating these results in other datasets, or comparing with different measures of GM or WM, such as cortical thickness or even structural connectivity computed from DTI tractography. Other extensions of dynamic fusion, including a 3-way fusion of GMV, FA, and dFNC could also be useful in further elucidating the varying linkages between GM/WM structure and time-varying brain function.

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