A DEEP-LEARNING APPROACH TO TRANSLATE BETWEEN BRAIN STRUCTURE AND FUNCTIONAL CONNECTIVITY

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ABSTRACT

While the majority of exploratory approaches search for correlations among features of different modalities, indirect/nonlinear relations between structure and function have not yet been fully investigated. In this work, we employ a neural machine translation model [1] to relate two modalities: structural MRI (sMRI) spatial components and functional MRI (fMRI) brain states estimated using a dynamic connectivity model. We consider each of the modalities as different "languages" of the same brain and fit a translation model to estimate a model for how structure influences function. Results identify multiple aligned aspects of brain structure and functional brain states showing significantly more or less alignment in the patient group as well as interesting links to other variables such as cognitive scores and symptom assessments. Our novel approach provides a new perspective on combining brain structure and function by incorporating indirect/nonlinear effects and enabling the algorithm to learn the interplay between structural and the functional networks.

Index Terms— multimodal fusion, deep learning, psychosis, schizophrenia

1. INTRODUCTION

Multimodal data fusion, combination of two or more types of data in a joint analysis, can reveal otherwise hidden information in neuroimaging related to brain illness [2]. Schizophrenia is a chronic illness that has served as a testbed for various fusion approaches [3]. Despite great progress, the field is still struggling with unraveling the complex brain changes associated with schizophrenia. Multivariate approaches have proven to be quite powerful, but most of these have focussed on linear relationships. To this end, we developed a novel nonlinear approach based on deep learning to investigate neuronal mechanisms underlying structure-function inter-relationships in patients with schizophrenia.

A number of psychosis-focused fusion studies have been published on the different approaches to brain imaging data fusion. A widely adopted method is *spatial overlap* that qualitatively describes the pattern of brain alterations from different modalities indicating information of brain pathologies [4, 5]. Recently, more informative data-driven approaches that fuse full data sets from different MRI modalities are receiving much attention as they make fewer assumptions about specific relationship among data sets [6, 7]. These methods typically extract *features* from each imaging type and search for variations in structure-function links in the feature space which simplifies the fusion strategy but enables one to study the full joint information among modalities including inference on indirect or direct structure-function relationships [8].

Motivated by the recent development of deep neural network based machine learning methods [9], we develop a multimodal fusion framework for brain imaging. A limitation of most of the existing multimodal fusion methods is that they only capture linear relationship between different modalities [7]. Recent work on deep learning for unimodal brain imaging has shown that deep belief networks (DBNs) can uncover potential hidden relationship and thus facilitate discovery [10, 11]. We hypothesize that gray matter variations might interact with the brain functional dynamics in an intricate way, and such relationships are buried in the data. In this work, we, therefore, utilize the ability of high level representation of deep models for discovery of brain structure-function links and evaluate the impact of mental illness on these links.

The proposed approach extends the idea of machine translation (in natural language processing) to find links between brain structure and function. Our view point is that sMRI and fMRI are different views/measurements of the same brain, and by analogy these 'different languages' convey common concepts or facts in different ways. The key ingredient of this novel approach is an "attention" module that learns an alignment between features of two different modalities similar to the deep machine translation model [1]. In our context, alignments are associations/links between time varying fMRI and static sMRI features. Because (sMRI) gives us an unordered set of features, we modify the model's attention mechanism to investigate brain structure-functional relationships thus moving it closer to caption generation models [12]. We also examine the learned alignments for group differences between healthy controls (HCs) and patients with SZ, as well as their relationships with cognitive scores.

Our method advances the state of the art in two distinct ways. First, to the best of our knowledge, this is the first study of deep multimodal learning in neuroimaging. Second, existing multimodal approaches consider functional aspect of imaging data in a static manner (but see [13]), while functional dynamics may convey important neuronal mechanisms of psychosis [14]. In contrast, our fusion approach combines sMRI features and dynamic functional connectivity features for finding variations across presumably hidden associations between brain structure and function.

2. METHODS AND DATA

We work with sMRI and fMRI data collected from 154 healthy controls (110 males, 44 females; mean age 37) and 144 schizophrenic patients (110 males, 34 females; mean age 38) at rest during eye closed condition at seven different scanning sites [14, 15].

Structural data: T1-weighted images were normalized to MNI space, resliced to $2 \times 2 \times 2$ mm, and segmented into gray, white, and CSF images [16]. Gray matter density (GMD) was analyzed with independent component analysis (ICA) to extract features as relationships among GMD regions [17]. 50 components were estimated

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using the group ICA of fMRI (GIFT) toolbox.[1] After a visual inspection and a stability analysis of the components, 23 were selected for further analysis.

Functional data: The motion corrected [18] despiked, warped to MNI atlas, and intensity normalized data were decomposed into components using spatial group ICA (GICA) in GIFT [19]. 47 temporally coherent intrinsic connectivity networks (ICN) were selected [14]. Pairwise correlation between ICN time courses were computed yielding a correlation matrix of size 47×47. To capture dynamics, correlation was estimated using a sliding window approach (see Damaraju et al. [14]) which we denote as dynamic functional network connectivity (dFNC). A discrete sequence of dFNC states were obtained using k-means clustering algorithm on the dFNC matrices, with a setting of $k = 5$ using the elbow criterion (see all of them in Figure 2).

2.1. Translation-based multimodal fusion model

Machine translation models that produce sentences in one language from another are common in the natural language processing discipline. Two languages convey a common concept or a fact in different ways with their own constructs, thus providing two views on the same underlying entity. We consider sMRI and fMRI as two different views of the same brain, and adopt a machine translation approach for the task of learning correspondences between these modalities.

We exploit the idea of attention mechanism proposed by Bahdanau et al. [1] to learn alignment (linkage) between dFNC states and brain structural components. However, unlike the sequence to sequence matching that attention solves in language translation, we match an unordered set of sMRI component loadings to temporally ordered dFNC states. To tackle this difference, we propose a modification to the attention network in our translation model. Figure 1A depicts different parts of our translation model in the context of neuroimaging

As shown in Figure 1A, two main parts of our translation-based fusion model are: (1) sequence predictor and (2) attention network. Input is an unordered set of structural component loadings of a subject, $\mathbf{x} = \{x_1, \ldots, x_j, \ldots x_J\}$, and the output is a temporally ordered dFNC state sequence, $\mathbf{y} = \{y_1, \ldots, y_i, \ldots y_T\}$, of the same subject. The information predictive of a sequence $\mathbf{y}$ may spread throughout the structural components expressed by coefficients $\mathbf{x}$, and it can be selectively retrieved by jointly training sequence predictor and attention network on a multimodal data.

Sequence predictor: The sequence predictor is a probabilistic model that predicts one dFNC state of a sequence at each time step, where we define each conditional probability as

$$p\left(y_i | y_1, \ldots, y_{i-1}, \mathbf{x}\right) = h\left(\mathbf{s}_i, \mathbf{c}_i\right), \tag{1}$$

where $\mathbf{s}_i$ is the current hidden state of a unidirectional recurrent layer and $\mathbf{c}_i$ is the current selective focus over structural components (*context*). The probability model of Eq. (1) embodies a fusion implicitly through conditioning on previous output history (from one modality) and the input (from the other modality). The time index i indicates dynamic property of one of data modalities. Right hand side of Eq. (1) captures the aspect of deep learning, i.e., the predictor works with latent representations of input and output as opposed to the direct input-output, which are learned from the data.

Eq. (1) is modeled by a feedforward neural network (NN)—a single hidden layer with a softmax output—stacked on top of a recurrent layer. At each time point, the recurrent layer computes the current hidden state $\mathbf{s}_i$ which is a function of the past state, previous output from the feedforward NN, and the current context, i.e.,

$$\mathbf{s}_i = g\left(\mathbf{s}_{i-1}, y_{i-1}, \mathbf{c}_i\right). \tag{2}$$

We use gated recurrent unit (GRU) [21, 22] to find a smooth trajectory in the latent representational space. Each output dFNC state y_i indicates one of the centroids of five clusters. Since the centroids are 47×47 matrices occupying a rather low dimensional subspace, we reduce the dimension to 4, i.e., $y_i \in R^4$, using principal component analysis (PCA). The current context $\mathbf{c}_i$ is described below.

Attention network is the most important part for our goal as it enables learning association(s) between functional dynamics and structural features. Just before i-th dFNC state is predicted, the attention network computes an alignment score (indicating strength of association) between the structural component x_j and dFNC state y_i. This score is based on recurrent state $\mathbf{s}_{i-1}$ and is evaluated for all structural components, i.e., $\forall j \in \{1, 2, \ldots, J\} \forall i$. For the attention module we use NN:

$$\mathbf{e}_i = \mathbf{V}^\top \tanh\left(\mathbf{W}_s \mathbf{s}_{i-1} + \mathbf{W}_x^\top \mathbf{x}\right) \tag{3}$$

$$\alpha_{ij} = \frac{\exp(e_{ij})}{\sum_{j=1}^{J} \exp(e_{ij})}, \text{ for } j = 1, 2, \ldots, J \tag{4}$$

$\mathbf{V}, \mathbf{W}_s$ and $\mathbf{W}_x$ are the parameters of the NN, and $\mathbf{e}_i$ is a length J vector containing unnormalized alignments. The normalized alignments are computed according to Eq. (4) and are interpreted probabilistically. The learned alignments modulate the structural components to obtain a context vector $\mathbf{c}_i$ at i-th time step as

$$\mathbf{c}_i = \boldsymbol{\alpha}_i \odot \mathbf{x} \tag{5}$$

where $\odot$ indicates element wise multiplication. In other words, the context vector serves as the currently focused structural components with their soft alignments. In effect, each alignment α_{ij} reflects the importance of structural component x_j with respect to previous hidden state $\mathbf{s}_{i-1}$ in deciding next state $\mathbf{s}_i$ and generating dFNC state y_i by the sequence predictor. Brain structure-function relationship is encoded in the alignments of their states, α_{ij}, for i-th dFNC state and j-th structural components.

The sequence predictor and the attention network are jointly trained using a gradient based optimization algorithm called *RMSprop* [23] optimizing the negative log-likelihood based cost function,

$$-\log(p(\mathbf{y}|\mathbf{x})) - \lambda \sum \alpha_{ij}^2. \tag{6}$$

In order to avoid the overfitting problem, we use L_2 regularization of alignments and a 50% dropout [20] in the hidden layers of the NNs (see Fig. 1A), while excluding dropout in the recurrent layer and inputs. Using a hold-out dataset, the number of hidden neurons in both feedforward NNs and in the recurrent layer is set to 50; the learning rate and the coefficient of L_2 norm to 0.01 and 0.5, respectively.

3. RESULTS

Alignments between dFNC states and structural components

Alignment scores for individual states are shown in Fig. 1C. In effect, each dFNC state has alignment scores across all 23 structural components and they sum to 1.00 (Eq. (4)). If equal focus or attention was given to every structural component, the alignment score would be 1/23 = 0.043. Besides, the alignment scores vary across

[1] http://http://mialab.mrn.org/software/gift/

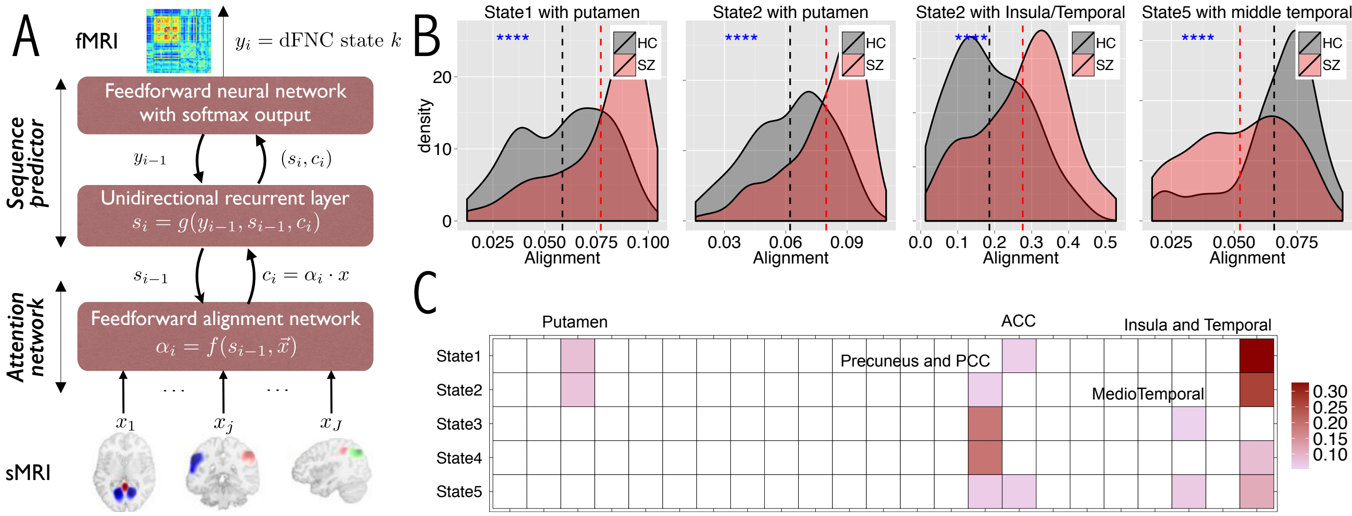

Fig. 1. A translation model for learning alignment between functional dFNC states and structural components. (A) Model structure. The attention network module is a feed forward network (input: 23, hidden: 50, output: 23) with a 50% dropout [20] in the hidden layer. The sequence predictor module has a recurrent layer (consisting of 50 gated recurrent units) and a feedforward network (input: $\{50{+}23 = 73\}$, hidden: 50, output: 5) with a 50% dropout in the hidden layer. The recurrent layer uses the dFNC correlation matrix as an embedding in the real vector space for the dFNC states. (B) Group differences in some paired alignments. The significances (FDR corrected) of Kolmogorov-Smirnov tests are provided as asterisks ('****': $p < 10^{-4}$). (C) Mean alignments across all subjects (both HC and SZ) thresholded at 0.057.

subjects for each dFNC state - structural component pair. Therefore, we show the mean alignments (thresholded at 0.056) across all subjects including HC and SZ in Fig. 1(A). States 1 and 2 where ICNs were sparsely connected had some similarity in their alignments, for example, both showed stronger associations with putamen and insula. On the other hand, state 3, 4, and 5 showed their associations with some of the structural components in the saliency and default mode networks (precuneus, PCC, and anterior cingulate cortex (ACC)), and in temporal cortex, in addition to the insula. In other words, the alignments for states 3,4, and 5 were more spread out than those for states 1 and 2, in addition to their regional differences across the brain.

The group differences in alignments are shown in Fig. 2. It should be mentioned here that no discriminating information of HC and SZ was supplied to the algorithm during training. To measure the significance, Kolomogorov-Smirnov tests were performed and the p-values are provided in each plot of Fig. 1(B). Mean alignments of states 1 and 2 with putamen were significantly higher for SZ patients. Healthy controls showed more alignments than SZ in the case of states 3 (not shown) and 5 with middle temporal gyri which is involved in various cognitive tasks. States 2, 3, and 5 also showed higher associations with precuneus and PCC for the healthy controls. Interestingly, most of the states exhibited significantly higher alignments with insula for the patients with SZ.

Relationships between alignments and meta-data

We examined the learned alignment scores to investigate their groupwise relationship with a cognitive score (attention/vigilance). This domain score was taken from van Erp et al. [24], which was based on the d-prime across blocks continuous performance test (CPT) z-scores. It measures how well a respondent discriminates between non-targets from targets. Figure 3 shows a linear regression fit between attention and vigilance score and alignments along with the p-values of significance test. Also shown are the relationships when each of the structural and functional features considered individually. The alignments of state 3 with middle temporal gyri revealed a strong positive correlation for the HC group, and those of state 5 with ACC showed a strong negative correlation for the patients with SZ. No such relationship, however, could be found when individual modality of data were examined. This clearly shows a benefit of taking multimodal approach because individual modality might capture only partial views.

4. DISCUSSION AND CONCLUSIONS

This study has proposed the use of a novel method of multimodal fusion for neuroimaging data with a particular goal of finding associations between brain structure and functional dynamics. The key idea is that, to some extent, information about dynamic fMRI features is spread over gray matter structural patterns, which can be selectively extracted using state-of-the-art machine learning techniques. To this end, we leverage the recent advancement of attention mechanism in deep learning to find (possibly nonlinear) alignments/associations between brain structure and function.

The dFNC patterns capture functional connectivity as a function of time. Analysis of the patterns by k-means clustering results in two major types of patterns. Among five clusters (states in Fig. 2), states 1 and 2 account for a weaker connectivity within the majority of ICNs and demonstrate no strong connectivity between subgroups (SC, AUD, VIS, SM, CC, DM, and CB). These are also the states wherein the patients with SZ made significantly more transitions than the HCs, suggesting a dysconnectivity in the SZ [14]. Our translation-based multimodal fusion approach adds an additional level of information revealing possible linkage of these states (1 and 2) with some of the brain structures. In particular, these states have stronger associations with insula and putamen. Correspondingly, insula has been shown to have a strong connection with

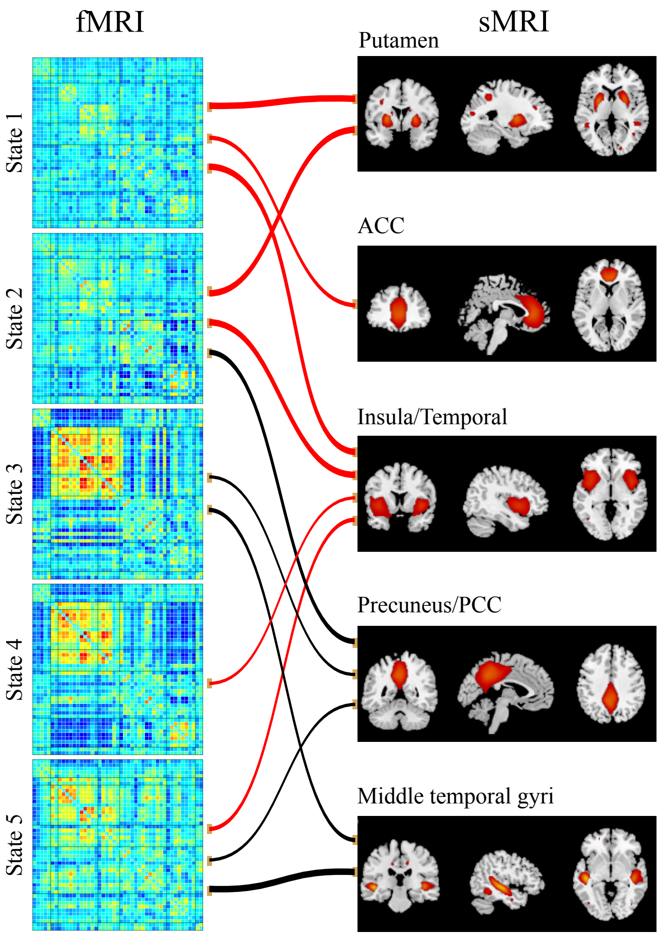

Fig. 2. Group differences in learned alignments between fMRI and SMRI features. A red link indicates higher mean for patients, black denotes higher mean for HCs. Significance of group differences are displayed as width of connections; the higher the significance, the wider the connecting lines between dFNC sates and structural components.

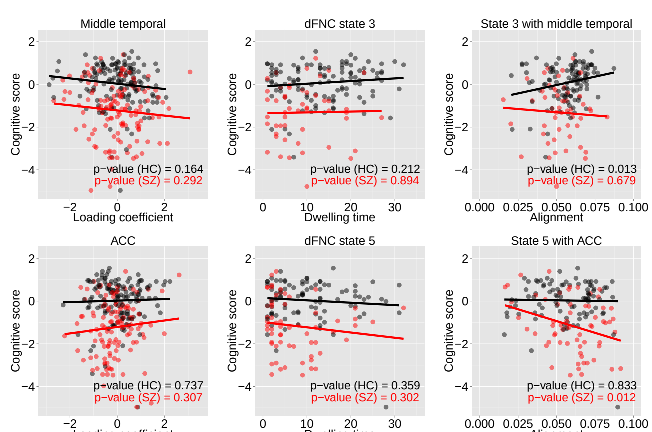

Fig. 3. Linear regression fit for attention and vigilance score with alignments (top panel: alignments of state 3 with middle temporal gyri and bottom panel: alignments of state 5 with ACC). Each plot is annotated with the significance level (p-value). Relationships with individual modality, structure and dFNC, are also shown in the left two plots of top and bottom panels.

aberrant activities in default mode and central executive networks in schizophrenic patients [25]. It also shows more gray matter volume loss compared to any other brain region in the patients with SZ. Parts of it are involved in the process of distinguishing between stimuli exogenous and endogenous with respect to the body, which gives it an obvious potential role in schizophrenia. Our findings of stronger associations between states 1(2) and insula are consistent with this finding as the states were occupied significantly longer by the patients with SZ. On the other hand, states 3, 4, and 5 speaks for high to moderate correlations among the several ICNs, including regions in AUD, VIS, and SM. Interestingly, the HCs made more transitions in these states. With regard to their associations with the brain structures, significantly more alignments are revealed with the GMDs in precuneus, PCC, and temporal cortex. Furthermore, comparing alignment distributions across structural components, states 3, 4, and 5 seem to be more evenly spread out than the states 1 and 2. This is expected because many ICNs showed stronger functional connectivity in states 3, 4, and 5. These distinctive new findings suggest potential advantages of our novel multimodal approach in the psychosis research.

Besides finding associations between brain structure and functional dynamics, we examined estimated alignments for their possible relationships to cognitive scores [24]. A strong positive correlation between attention and vigilance score and alignment of state 3 with middle temporal gyri, for the HCs, was revealed only when multimodal fusion was adopted. Neither of unimodal features indicated such relationship. Likewise, a strong negative correlation for the patients with SZ was found between their cognitive scores and alignments of state 5 with ACC, while unimodal features failed to provide such information. The positive correlation in the HCs and negative correlation in the patients suggests distinct structure-function mechanisms, thereby demonstrating an interplay between deficits and dysfunction in the patients. The observed relationships are consistent and extend previous reports on structure-function abnormalities in patients with SZ [6, 26].

Although it is generally believed that structure and function in psychotic disorders are associated in complicated ways, the majority of researchers still resort to linear models in their work. The main reason is an expectation that information in the nonlinear signal is weak or hard to capture. In this paper we demonstrated evidence that, with an appropriate method, nonlinear interactions can be reliably extracted and that they carry otherwise not-detectable information that discriminates between schizophrenia and healthy controls. The ability to capture nonlinearity, however, is not the only strengths of the approach. Importantly, the model is able to perform data fusion of dynamic (sequential) and static modalities, whereas in many existing data fusion approaches the dynamic modality needs to be manually compressed into a static representation in a pre-processing step. This property of our approach allows learning from variation in dynamics within and across subjects and results in a new discriminative dimension for schizophrenia patients and controls that could potentially enhance our understanding of the disorder. We conclude that the deep learning based nonlinear machine translation approach has a high potential for analysis of multimodal data thanks to its flexibility and representational power.

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