

A CONTRASTIVE LEARNING-BASED APPROACH TO MEASURE SPATIAL COUPLING AMONG BRAIN NETWORKS: A SCHIZOPHRENIA STUDY

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ABSTRACT

Resting-state functional magnetic resonance imaging (rs-fMRI) has become a widely used approach for detecting subtle differences in functional brain fluctuations in various studies of the healthy and disordered brain. Such studies are often based on temporal functional connectivity (i.e., the correlation between time courses derived from regions or networks within the fMRI data). While being successful for a number of tasks, temporal connectivity does not fully leverage the available spatial information. In this research study, we present a new perspective on spatial functional connectivity, which involves learning patterns of spatial coupling among brain networks by utilizing recent advances in deep learning as well as the contrastive learning framework. We show that we can learn domain-specific mappings of brain networks that can, in turn, be used to characterize differences between schizophrenia patients and control. Furthermore, we show that the coupling of intra-domain networks in the controls is stronger than in patients suffering from the disorder. We also evaluate the coupling among networks of different domains and find various patterns of stronger or weaker coupling among certain domains, which provide additional insights about the brain.

Index Terms— Contrastive learning, spatial coupling, resting-state fMRI, ICA

1. INTRODUCTION

Schizophrenia (SZ) is a psychotic disorder that is thought to be linked to dysconnectivity in the brain [1]. This disorder often cooccurs with symptoms including delusions, hallucinations, social isolation, and disorganized behavior. The disease impacts individuals worldwide¹, and as a lifelong disorder, it is one of the most disabling, existing treatments have many side effects, and there is no cure. A significant amount of effort has been pursued in clinical and research entities to discover the cause(s) and characteristics of SZ to

enhance the chance of early detection and developing more effective treatments. Because schizophrenia is a brain disorder, there is much focus on brain imaging modalities (e.g., fMRI) and statistical analysis methods for identifying brain networks.

During the past decade, fMRI has become one of the most widely used neuroimaging techniques in SZ studies. Many research studies have tended to work with resting-state fMRI (rs-fMRI), where subjects are at rest during their scan². This is because rs-fMRI scans are more easily performed in patients across a range of ages, and there are many existing data analysis pipelines [2]. An fMRI scan provides a map of functional activity in the brain that can be later used with statistical and mathematical approaches to estimate *functional networks*. Two of the most well-established approaches are seed-based analysis and independent component analysis (ICA). While seed-based approaches are widely used and relatively straightforward to implement, ICA has several advantages over seed-based approaches. First, ICA is a data-driven method in the sense that it adapts to the individual subjects and ensures temporally coherent voxels. Second, ICA provides both spatial maps and their corresponding time courses. And finally, ICA components can overlap, which allows for separation of artifacts from signal as well as for capturing multiple overlapping but distinct signals of interest.

Many rs-fMRI studies have investigated group differences in interactions between functional networks by comparing functional brain connectivity (FNC³) of SZ to control (CN) groups [3]. They have discovered increased or decreased connectivity in certain regions of the brain for SZ individuals. For example, some papers have reported the default mode network (DMN), a widely studied network associated with internal reflection, has been linked to hypo-connectivity in SZ [4], [5]. Several other studies have noted decreased connectivity within salience networks (SN) [1] and between thalamus and cerebellum networks [6] as well as between visual and sensory-motor networks [7] for SZ, while

¹ About 1% of the population worldwide suffers from schizophrenia.

² Other studies have used task-based fMRI studies (where the subjects are instructed to follow/perform certain task), although the rs-fMRI is more common.

³ The correlation between time courses.

others have observed increased connectivity among thalamus and sensory networks [6] in SZ versus CNs.

While such work has focused on temporal connectivity among regions (functional connectivity; FC) or among networks/components (functional network connectivity; FNC) to identify dysconnectivity in the brain, in our research, we investigated the relationship among spatial maps (i.e., spatial coupling) to recognize functional networks coupling that contributes to the SZ disorder. Our method is based on a novel deep learning-based architecture that generates domain-specific embeddings of ICA-driven spatial maps in a supervised contrastive learning setting.

2. METHOD

Concisely speaking, our approach employs the contrastive learning framework to extract embeddings for spatial maps, which are later used to measure the coupling between brain networks. As such, the proposed model is comprised of two important components, an embedding network, and an L1-based distance metric. The task of the embedding network is to generate domain-specific embeddings of the functional networks in such a way that similar networks (i.e., networks of the same domain) are mapped to closer points in the embedding space and at the same time farther from networks that belong to different domains. Once the samples are mapped into a space where the abovementioned objective is fulfilled, we use an L1 distance to quantify how similar or dis-similar each pair network would be.

2.1. The embedding network

Our embedding network is based on the 3D-ResNet10 [8] architecture, which receives 3D input images and generates 512 high-level features⁴. This model is a reduced version of the original Resnet model, which replaces 2D CNN components (i.e., convolutional kernels, pooling and batch normalization layers, etc.) with their 3D counterparts and removes the layers that do not contribute significantly to the performance. This makes such a model trainable on moderate GPU memories. To better capture complex non-local relationships between features, we augmented this model with a multi-layer perceptron [9] with a 512-dimensional hidden layer and a 128-dimensional output layer⁵. Fig. 1 visualizes a high-level view of our proposed model. In summary, this model leverages the residual networks as well as the multi-layer perceptron to generate 128-dimensional embeddings of ICA-generated spatial maps for downstream analysis.

To learn domain-specific embeddings of spatial maps efficiently, we used the supervised contrastive learning framework [10]. This allows extraction of within and

between-domain informative embeddings. Because the contrastive loss requires pairs of samples, we pair each spatial map of a given subject with another map of the same domain but a different subject. For any given domain, the contrastive loss considers all such pairs that belong to the same domain as positive pairs, and the rest are regarded as negative ones. Once this model is trained using the contrastive loss, the resulting embeddings can serve as a domain-informed representation of each input network.

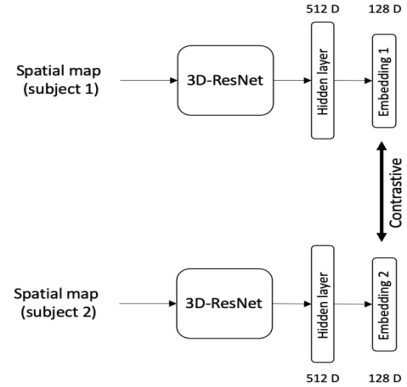


Fig. 1. The architecture of the proposed model.

2.2. The L1-distance layer

The supervised contrastive learning framework makes it possible to learn rich embeddings of spatial maps. Now to compute the distance between each pair of networks in the resulting space, we compute the L1 distance (i.e., the sum of the absolute difference values of two embeddings) as it has been shown to serve as a robust dissimilarity metric before. This final distance can now be regarded as a measure of spatial coupling between the functional brain networks of interest. A large distance corresponds to networks that have weak spatial couplings, while low distance pairs represent strong couplings between networks.

3. EXPERIMENTAL DATA

We studied resting-state fMRI data from 2,115 individuals, including 1,060 healthy control (CN) and 1,055 schizophrenia (SZ) patients. The data are aggregated across five multi-site studies. We applied spatially constrained ICA using the NeuroMark pipeline [11] to generate 53 subject-specific functional networks from 4D rs-fMRI images. The NeuroMark approach is a hybrid between data-driven ICA and model-based approaches, which leverages spatial priors are adapted to individual subjects to provide a fully automated ICA framework. The functional networks were grouped into seven domains, namely, subcortical (SC),

⁴ We modified the ResNet model in [8] (<https://github.com/kenshohara/3D-ResNets-PyTorch/blob/master/models/resnet.py>)

⁵ The size of the last two fully connected layers is selected based on [10]; however, we replaced the 2048-dimensional layer with a 512-dimensional embeddings layer to fit our data into GPUs.

auditory (AU), sensory-motor (SM), visual (VI), cognitive control (CC), default mode (DM), and cerebellar (CB) domain (see Fig. 2), according to [12].

4. EXPERIMENTS AND RESULTS

To evaluate our model in an unbiased way, we split our data into training, validation, and test sets, such that the data corresponding to no two subjects appears in more than one set. Furthermore, we perform a max-min per-image normalization on each spatial map. To counter the overfitting effect, stratified 5-fold cross-validation where the number of healthy and SZ patients remain roughly the same across each fold. We trained our model with a learning rate of 0.01 and batch size of 2500 samples for 100 epochs. We used early stopping with a patience of 20 to avoid overfitting. The contrastive loss temperature in our experiments was set to 0.01.

We implemented our model using the PyTorch deep learning library and trained it on eight NVIDIA Tesla V100 GPUs, each with 32GB of RAM, in parallel. The overall training time for each fold took ~ 8 hours on our local cluster. Fig. 3 (right) visualizes the convergence curve of our model on the test sets.

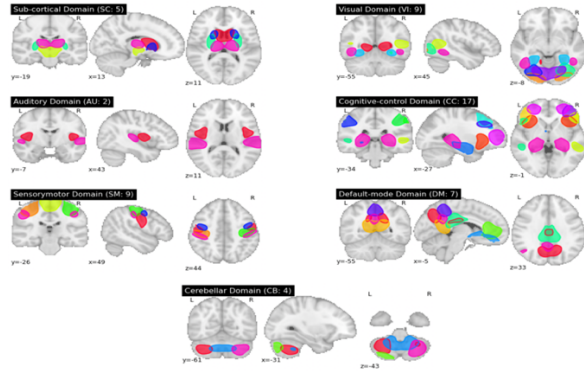


Fig. 2. ICA-driven functional networks.

4.1. t-SNE visualization

We visualized the embeddings of spatial maps learned by the model using the t-SNE visualization. Fig. 3 (left) shows that our model has a strong capability in differentiating brain networks that belong to different domains. This means our model can efficiently map networks into a new space in which networks of the same domain are close together while other networks of different domains are far apart.

4.2. Spatial couplings heatmap

Fig. 4 shows the heatmap of the difference in L1 distances between the schizophrenia and control groups. According to the figure, intra-domain networks, especially subcortical and default mode domains, in SZ subjects have significantly

larger distances than normal controls. A larger distance suggests a lower strength of spatial coupling in schizophrenia subjects compared to the control group. Furthermore, we observe that networks of each domain interact strongly in different ways with other domains across the two groups. This is especially the case for subcortical networks. In other words, while the subcortical networks in the SZ cohort have stronger spatial coupling with visual and cerebellar networks than NC, they have weaker coupling with sensory-motor and cognitive-control networks.

To test for the significance of the abovementioned results, we applied a two-sample t-test to the L1-distance mean between the two cohorts. In Fig. 4, the upper triangle shows the pairs that are statistically significant (i.e., corresponding p-values < 0.05). Accordingly, the majority of the network pairs show significant differences. This is particularly the case for the subcortical and default mode networks when paired with other networks.

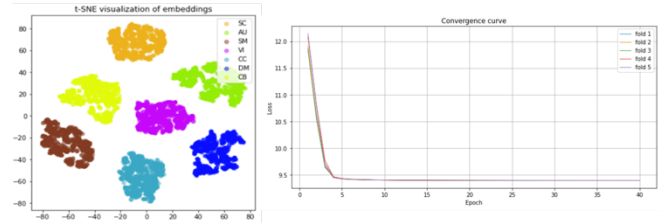


Fig. 3. t-SNE visualization of embeddings (left) and convergence curve (right).

5. DISCUSSION

Overall, our results suggest that the spatial coupling between functional brain networks computed by ICA turns out to be significantly different between SZ and NC subjects in most cases. We observe a significantly lower coupling within default mode networks, which is consistent with previous findings that report a decreased functional connectivity [1], [5]. This observation suggests that coupling between DMNs is disturbed when a subject is engaged with stimulus-independent thoughts [13], such as thinking about himself or his past/future. Furthermore, we observe significant hypo-coupling, i.e., decreased spatial coupling, in SC-CB (which is consistent with [6] that reports decreased coupling between thalamus and cerebellum), SC-VI, SM-VI (which is consistent with [7] that reports disconnection between visual and sensory-motor networks), and DM-CB networks, and hyper-coupling, i.e., increased spatial coupling, in SC-SM (which is consistent with [6] that reports thalamo-sensory increased coupling) and SC-CC networks, and nearly no difference between CC-CB networks in SZ comparing with NC.

Last but not least, we should note that when training our model, we are not using the diagnostic labels of the subjects in any way, yet when we compute the distance between embeddings, we see a clear pattern that depends on such

labels. This corroborates the success of the proposed model in finding informative and insightful representations of the underlying networks when using contrastive learning to learn the model parameters.

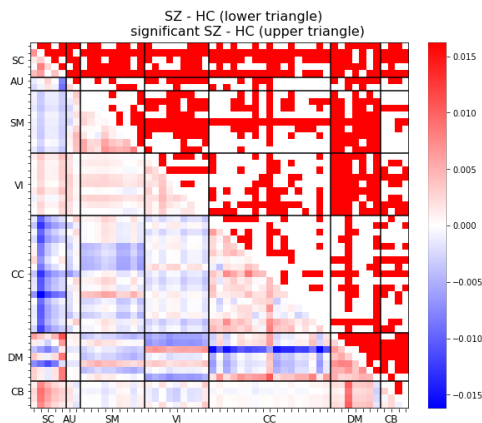


Fig. 4. Heatmap of differences in L1 distance between schizophrenia and control groups (SZ - NC).

6. CONCLUSION

In this study, we proposed a deep learning-based framework to compute the spatial coupling between functional brain networks of rs-fMRI images. We utilized the contrastive learning framework to generate domain-specific embeddings of the networks such that networks of the same domain become closer in the embedding space than networks of different domains. We further showed that such embeddings are informative enough that can reveal the network-network couplings with the use of a simple distance metric such as the L1 distance. We used SZ as the case study and showed that it serves as a proof of concept for our proposed approach in a statistically significant way. Furthermore, our findings showed that schizophrenia patients can be characterized by hypo-coupling within the SC and DM networks and in SC-CB and SC-VI networks in a statistically significant way. On the other hand, we observed hyper-coupling between SC-SM and SC-CC networks. Finally, it remains to be seen if such an approach can help us gain interesting insights about other types of brain disorders such as Alzheimer's and Parkinson's disease and to see if brain networks coupling can be used as a non-invasive biomarker.

7. COMPLIANCE WITH ETHICAL STANDARDS

This is an academic study for which no ethical approval was required.

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