Alzheimer’s disease classification using CNN over structural connectomes

Editors: Under Review for MIDL 2020

Abstract
In the following work, we use a deep convolutional neural network (CNN) trained on the diffusion weighted MRI (DW-MRI) tractography connectomes of patients with Alzheimer’s Disease (AD) and Mild Cognitive Impairment (MCI) to better understand the connectomics of that disease progression. The CNN is tailored to the brain structural connectivity matrix and we use it to highlight specific regions related to AD, depicted from the discriminative power learned from the trained model. Most of the connected regions with high structural differences between groups are also reported in AD literature. Our findings, support that deep learning over structural connectomes is a powerful tool to leverage the complex structure within connectomes derived from diffusion MRI tractography. To our knowledge, our contribution is the first application of deep learning algorithms for AD prediction using structural connectomes. Our work gives new insights into the structural connectivity that drives the AD pathology.

Keywords: Structural connectome, diffusion weighted MRI, deep learning, saliency maps, Alzheimer’s Disease

1. Introduction
Early detection of neuro-degenerative diseases like Alzheimer’s Disease (AD) along with proper treatments can delay its progression (Livingston et al., 2017; Weller and Budson, 2018). Several approaches have been explored to better predict, detect and understand the disease. These approaches include biological markers (Hampel et al., 2008; Kapaki et al., 2007; Irizarry, 2004; Blennow et al., 2015; Patel et al., 2011; Zetterberg, 2008; Mattsson et al., 2009; Gomar et al., 2011; Gomez-Isla and Frosch, 2019), blood-based bio-markers (Henriksen et al., 2014; Thambisetty and Lovestone, 2010; Mayeux and Schupf, 2011; Doecke et al., 2012), neuro-psychological tests (McKhan et al., 1984; Tierney et al., 2005; Jacobs et al., 1995; Weintraub et al., 2012), artificial intelligence algorithms on medical images (Liu et al., 2014; Moradi et al., 2015; Li et al., 2019; Jo et al., 2019; Lee et al., 2019; Litjens et al., 2017; Liu et al., 2018). Besides, magnetic resonance imaging (MRI) has been a modality of choice for AD diagnostic and has demonstrated its significance (Vemuri and Jack, 2010). Most MRI-based techniques for studying AD can be grouped under two main categories of analysis: i) MRI anatomical images analysis and ii) structural and functional connectomes (connectivity matrices) (Contreras et al., 2015). Standard techniques employing MRI can be distinguished between: clinical analysis (Engelborghs, 2013; Cummings et al., 2019), segmentation techniques (Biju et al., 2017) and machine/deep learning algorithms (Jo et al., 2019). In this work, we focus on deep learning classification using the structural connectome derived from diffusion weighed MRI.
In structural and functional connectivity analysis, the human brain complexity is represented as an interconnected network. This connectome can be represented as graphs, where nodes are brain anatomical regions and edges are connectivity “strength”. Several studies explored brain networks using functional imaging modalities (Prescott et al., 2014; Filippi et al., 2018). The knowledge and characterization of this connectome, and underlying changes in brain structure and activity, is essential to study cognitive and behavioral impairments. However, previous AD prediction rely on manually chosen characteristics and none include DW-MRI tractography structural connectivity estimation.

In this work, we intend to explore to what extent a deep convolutional neural network trained on the connectome of a large number of ADNI subjects can help underline the characteristics of the AD structure (adni.loni.usc.edu). In that perspective, we trained a modified version of the BrainNetCNN (Kawahara et al., 2017) on the connectivity matrices of an heterogeneous set of patients to predict three groups of subjects: normal control (NC), mild cognitive impairment (MCI) and AD. Then, with the help of visualization techniques and a thorough node ablation analysis, we get to visualize brain regions as well as their connectivity that are involved in the prediction of AD.

Our overarching objective with this work is to use deep learning as a tool to leverage the complex structure within DW-MRI connectomes and give new insights to connectomics approach in AD. To our knowledge, this is the first time such a study is made.

2. Methods

Since structural connectomes from DW-MRI tractography contain edge weights between pairs of regions, it can easily be represented by a 2D matrix of all connections (Jeurissen et al., 2019). This matrix is an adjacency matrix $A$ of size $N \times N$, where $N$ is the number of regions and $A_{ij}$ is the weight between regions $i$ and $j$. While this connectivity matrix can be pictured as a 2D image (c.f. Figure 1 for an example of a connectivity matrix), it cannot be inputted directly into a regular convolution neural networks (CNN), as the local neighborhood around each element $(i,j)$ is not isotropic. This is due to the very nature of a connectivity matrix, where neighbors of a node are distributed along horizontal lines and columns, i.e. connections to different brain regions.

As such, we implemented a modified version of BrainNetCNN (Kawahara et al., 2017), whose original use was to predict cognitive and motor activities in premature infants. This network implements two convolution filters adapted to the context of a connectivity matrix: a so-called edge-to-edge (E2E) filter and an edge-to-node (E2N) filter.

**Edge-to-Edge (E2E) and Edge-to-Node (E2N) layers**

By definition, each region $i$ of a symmetric adjacency matrix $A$ is connected to all elements in the $i^{th}$ row ($A_i$) and $i^{th}$ column ($A_i$). As such, it is not related to its local neighbors like a pixel of a regular image would be. Thus, if such adjacency matrix is to be processed by a CNN, the usual 2D convolution operation need to be redefined. In that perspective, the E2E filter is made of two 1D convolution filters: one spanning along the rows of $A$ and one spanning along the columns of $A$ (c.f. figure. 1 for an illustration). This simple, but
effective operation, filters the topological locality of brain networks, combining weights of connected edges. The output of this convolutional layer is a set of $M$ feature maps.

After the E2E layer comes the E2N layer. The E2N filters extract features from all the weights in each row in the preceding feature maps and convert it into a single scalar. The E2N layers captures the second order connectivity (indirect connections) of the brain. As shown in figure 1, the E2N layer is formed of $L$ filters and thus returns $L$ vectors of dimension $N \times 1$. We implement this operation with a 1D convolution filter.

**The proposed architecture**

Our proposed network architecture is formed of an E2E layer followed by an E2N layer and two fully-connected (FC) layers. The E2E and E2N layers operate as hierarchical brain networks feature extraction functions. Note that for better convergence during training, a batch-norm operation was added at the end of each layer. These layers are then followed by two FC layers and then the output layer. To obtain a binary classification (e.g. NC-AD), a *sigmoid* function is added to the output layer. Otherwise, for a three-class prediction (NC-MCI-AD), a *softmax* function is used at the output.

![Figure 1: The BrainNetCNN-like architecture of our method.](image)
HpBandSter algorithm was used to fine-tune the model’s hyperparameters including the number of E2E and E2N filters and the activation function (ReLu or LeakyReLu). This algorithm relies on Falkner et al. (2018) algorithm which combines both HyperBand (Li et al., 2017) and Bayesian optimization algorithm.

The final best architecture is formed of a E2E layer with 23 filters and a LeakyReLu activation function with a negative slope of 0.015976 followed by an E2N layer with 59 filters with a ReLu activation function. Meanwhile, the FC layers each contain 19 units, the learning rate is 0.007812 and the batch size is of 25. Subsequent good configurations among the other possible ones are reported in the appendix.

Training

The proposed architecture was implemented using Pytorch with the use of HpBandSter, to optimize all hyperparameters. In order to ensure that configurations with best performance were retained, 10 fold cross validation was utilized. The loss function is the well-known cross-entropy which we minimize with the Adam optimizer. For the learning procedure, along with the 10-fold cross-validation, the dataset was split into three sets: training (70%), validation (15%) and test (15%).

3. Dataset

To train our network and subsequently analyze the AD connectome, the ADNI (Alzheimer’s Disease Neuroimaging Initiative) dataset was used (Iwatsubo, 2011). Different releases of ADNI exist. Here, ADNI2 and ADNI-Go were used with clinical-like DW-MRI acquisitions with 41 directions, 2mm isotropic and b-value 1000 s/mm². In order to compute the tractography from DW-MRI, Theaud et al. (2019) pipeline with default parameters was employed, ensuring reproducibility and fast processing. Connectivity matrices were estimated from tractography using the “Lausanne 2008” brain parcellation, an atlas of anatomical regions (Dale et al., 1999; Hagmann et al., 2008), and streamline count between every pair of regions (see Figure 1).

After quality control sanity checks, the final dataset is formed of 480 connectivity matrices distributed as follows: 152 NC, 181 MCI and 147 AD. Meanwhile, the baseline sample is formed of 57 NC, 95 MCI and 34 AD. These connectivity matrices represent an undirected (symmetric) complete weighted graph of dimension 83 × 83. It is worth mentioning that connectivity matrices were normalized, summing to 1, in such a way that each element of the matrix represents a probability of connection occurring between region i and region j in the brain. The Figure 1 (bottom-left) presents a connectivity matrices from DW-MRI tractography with cortical regions.

Furthermore, it is known that streamline count between regions is heavily dependent on the size or surface area of cortical regions (Girard et al., 2014). Hence, the local volume of each cortical region were added in the previously generated connectivity matrices. In order to obtain the connectivity matrices with the cortical volume, the diagonal of the initial connectivity matrices has been filled with cortical volume of each region. This diagonal was also normalized, summing to 1, resulting in reconstructed connectivity matrices with a
total sum equal to 2. As a result, our experiments were tested for both types of matrices, with and without cortical region volume in the diagonal.

4. Experiments
As mentioned before, in this paper we hypothesize that the use of a trained neural network can help us better understand the AD connectomics. We do this through two experiments: 1) an ablation analysis to measure to which extent a region and/or an edge can affect the prediction of the neural network and 2) a visualization experiment to recover which areas of the brain drive the most the output of the neural network.

Regions and connections ablation analysis
The main idea here is to change the connectivity between regions of the brain in order to evaluate the impact of that change on the overall performance of the model. For this, three approaches were implemented: a node ablation, a node randomization and an edge ablation. The node ablation forces to zero every connection between a region $i$ and every other regions. The node randomization “randomizes” values of connectivity between a region $i$ and the other regions while keeping the same average instead of forcing them to zero. As for edge ablation, we set to zero the connection between regions $i$ and $j$. This last approach is also tested with a combination of edges, to a maximum of 4 connections. The ablation analysis is done in turn for each region and each edge.

Saliency map extraction
The goal of the ablation analysis is to identify if a node or an edge is responsible on its own for certain predictions of the network. In this section, we want to identify if a group of nodes or edges is responsible for certain outputs of the neural net. Hence, a legitimate step to understand the regions driving the model prediction is by retroprogating the gradient from a maximally activated output neuron all the way to the input connectivity map $A$. We did so after training the network to discriminate between NC, MCI and AD. The magnitude of the gradient shall thus give us a clue on which combination of regions and edges are most important for predicting these classes.

For interpretability and explainability of the results, advice from an expert in the field are included in the discussion. Hence, the interpretation will depend on the resulting features visualized over averaged inputs for each class and knowledge from the AD literature.

5. Results
Results given in this section are from the learned model applied to the test set, after training and validation, including a 10 fold cross-validation. The accuracy of the one-to-one prediction are as follow: 78% for NC-MCI (45 test samples), 91% for NC-AD (45 test samples) and 81% MCI-AD (49 test samples). Table 1 summarizes the one-to-one predictions with the following metrics: prediction precision, recall, F1-score, accuracy of training, validation and test. For both datasets: with and without cortical volume for each region in the diagonal (Table 1). For the one-to-all prediction, NC-MCI-AD (72 test
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samples), when incorporating cortical region volume in the diagonal of the matrices, the score improves from 76% to 78%.

<table>
<thead>
<tr>
<th>Prediction</th>
<th>Cortical regions volume</th>
<th>precision</th>
<th>recall</th>
<th>F1-score</th>
<th>valid acc.</th>
<th>test acc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC - MCI</td>
<td>no</td>
<td>86%</td>
<td>70%</td>
<td>77%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>NC - AD</td>
<td></td>
<td>95%</td>
<td>86%</td>
<td>90%</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>MCI - AD</td>
<td></td>
<td>78%</td>
<td>81%</td>
<td>80%</td>
<td>71%</td>
<td>81%</td>
</tr>
<tr>
<td>NC - MCI</td>
<td>yes</td>
<td>74%</td>
<td>74%</td>
<td>74%</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td>NC - AD</td>
<td></td>
<td>91%</td>
<td>91%</td>
<td>91%</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>MCI - AD</td>
<td></td>
<td>80%</td>
<td>90%</td>
<td>85%</td>
<td>75%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Table 1: Reported metrics for the experiments with and without regions volume.

Regions and connections ablation analysis

To our surprise, shutting down nodes and edges did not decreased in any significant way the predicted scores. In addition, the node randomization decreased our prediction accuracy by only 0.5%.

Saliency map visualisation

As mentioned before, we retropropagated the gradient from the maximally activated output neuron associated to AD, MCI and NC. Regions with higher values in the AD and MCI saliency maps are: hippocampus, amygdala, parahippocampal, entorhinal, fusiform regions.

To further illustrate the difference between the activated regions of AD, MCI and those of NC, we subtracted the NC saliency map from the AD and the MCI. We did so with the purpose of underlying the specifics of the AD and MCI connectomes. The subtracted saliency maps are illustrated in Figure 2. This revealed that the entorhinal was the most intense difference between AD and NC along with hippocampus for MCI and NC. These regions are reported in AD research from voxel-based morphometry, cortical thickness or functional connectomics (Jhoo et al., 2010; Choo et al., 2010; Pennanen et al., 2004; Hojjati et al., 2017).

6. Discussion

We have shown that CNNs adapted to the structure of DW-MRI tractography connectomes can be used to classify MCI and AD afflicted brains. Moreover, we showed that our trained network could be used to gain insights into the structural connections that drive the AD pathology.

AD prediction

Previously reported results for MCI and AD prediction are in the order of 80%, e.g. 60%-70% from with MRI morphological method (Lisowska et al., 2019), and from 80%-90% with
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Figure 2: Saliency map features visualisation resulting from the difference of two saliency map generated with the one-to-all model: A) MCI minus NC, B) AD minus NC. Diagonal intensity in the diagonal are presented with node color, and other values represented with edge color. Red circle is around the hippocampus node, and green circle for the entorhinal region, two regions known for their implication in AD.

Our work shows competitive prediction percentages and also emphasizes that the key challenge in AD prediction is the prediction between MCI and AD, and between NC and MCI. These are the hardest classification tasks, where disease prediction is not clear cut, and most likely requires more information (multi-modality, genetics, amongst others).

### Regions and connections ablation analysis

The results of the ablation procedure support the idea that not only a single region, and its connections, are responsible for AD prediction, but the combined effect of several cortical regions, that are directly or indirectly connected via long-range fiber tracks. By indirect connectivity, we mean that a 2nd order connectivity exists between these regions. DW-MRI tractography is the only non-invasive modality that can provide this structural connectivity brain architecture, which is essential and should be considered in future AD studies.

### Saliency map visualization

The amplitude of the retropropagated gradient underlines which regions strongly correlate with the neural net prediction. However, this correlation could be explained by a lower or higher structural connectivity estimated from the DW-MRI thus the analysis of the saliency map should be interpreted with care.

### Limitations and future directions

One of the current limitations of our work is the absence of anatomical prior in the structural connectome reconstruction. As such, more insights from the disease along with anatomical constraints could improve results. Since incorporating cortical region volumes can improve
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the prediction, adding more information from relevant brain features could furthermore increase the model power. For example, more information from diffusion such as fractional anisotropy (FA), mean diffusivity (MD), as well as more information from other MRI contrasts (e.g. cortical thickness, myelin, functional connectivity). As a result, future direction in predicting AD, and its progression with MCI, is within the application of advance geometric or graph CNN over the connectome (Bronstein et al., 2017). Furthermore, along with continuous progress and efforts in creating larger datasets, a regression problem for AD progression prediction could be formulated, so that disease progression can be assessed as a continuum in time.

7. Conclusion

Structural connectomes from DW-MRI tractography contain rich information about underlying anatomical architecture of the brain. The proposed neural network architecture is useful to extract features within brain connectomes that predict the AD pathology. Our methodology confirms that a network of direct and indirect long-range structural connections may drive disease progression and need to be further studied with complimentary information in the future. This could have important implications in neuro-degenerative diseases analysis.

References


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