The Brain Train: Analysis of Alzheimer's Brain Structures Using Machine Learning

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Table of Contents

Abstract

Connectomes describe the way clusters of neurons are interconnected within the brain. Pathways of neurons interconnect clusters to form a network, which is difficult to process in medical imaging with the naked eye. We focused on the Anterior Cingulate Area and the Retrosplenial Area, two areas in the default mode network (DMN). The DMN is a set of brain regions with low-frequency correlated activity in the absence of a goal-directed task and is particularly vulnerable in Alzheimer's disease, Autism, and Schizophrenia. Our goals were to create an accurate computational framework that can reliably distinguish between parts of the connectome - from brain regions to neuron cell types and to quantify the anatomy of the brain and the variability of individuals and disease states. Using Python libraries, we collected data, transformed it into processable information, and “trained” a deep neural network to classify images based on areas and cell types. We used Allen Brain Atlas, a comprehensive database of projection mapping experiments in mice brains. These were conducted with viral tracers containing Green Fluorescent Protein under a two-photon micrograph. We created two convolutional neural networks, which functioned as binary classifiers based on brain areas and cell classes. Our networks successfully classified unlabeled images with 94% and 92% accuracy. With this, our neural network gives us a novel method to quantify the anatomy of the brain and the variability across individuals and can be used as a powerful model to test for alterations of diseases, in the largely unexplored areas of the brain.

Introduction

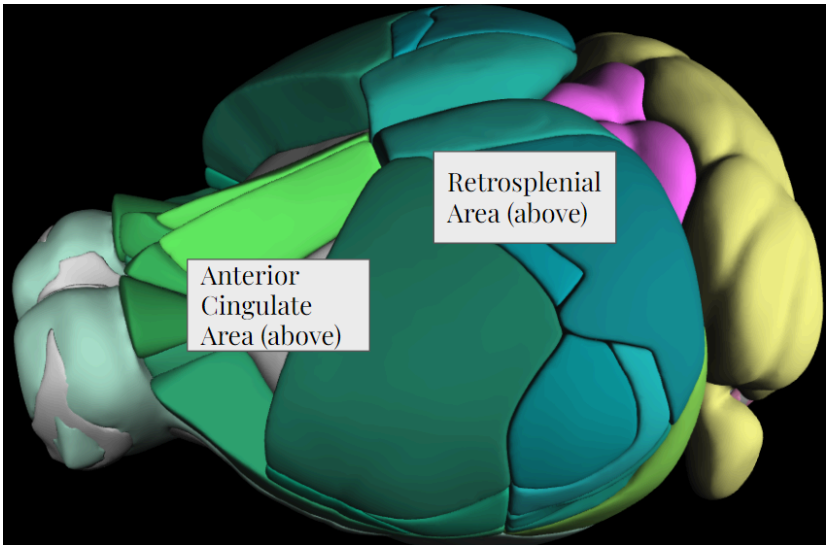
Within the field of neuroscience, the structure and function of various parts of the brain are still widely unknown, especially information about how neurological diseases affect various parts of the brain. The field of connectomics studies the way in which clusters of neurons are interconnected within the brain. An important concept within connectomics is excitatory neuron classes, which include the three primary types of intratelencephalic (IT), pyramidal tract (PT), and corticothalamic (CT). These classes project to different areas of the brain, and can be studied for a more detailed analysis on the effect of neurological diseases on the brain.

Pathways of neurons connecting different clusters to form networks within the brain, which cannot be easily processed by existing medical technology. The brain is divided into several different regions each performing different functions. Large-scale brain networks allow for perception of senses, cognition, and motor output.

Certain networks known as resting state (rs) networks tend to have less well-defined functions and are characterized temporally correlated intrinsic activity. The Resting State (RS) Default Mode Network (DMN), which can be visualized through magnetic resonance imaging, is an anatomically distributed set of brain regions with low-frequency correlated activity in the absence of a goal-directed task.

DMN analogs have been seen across many mammalian species, and their consistency suggests that they play a role in organizing healthy brain activity. The DMN is particularly vulnerable in Alzheimer's disease. The DMN also reflects the effects of other disorders such as Autism and Schizophrenia. Studying brain regions within and outside of the DMN is important to ascertaining and assessing the effects of neural diseases like Alzheimer’s. The Retrosplenial

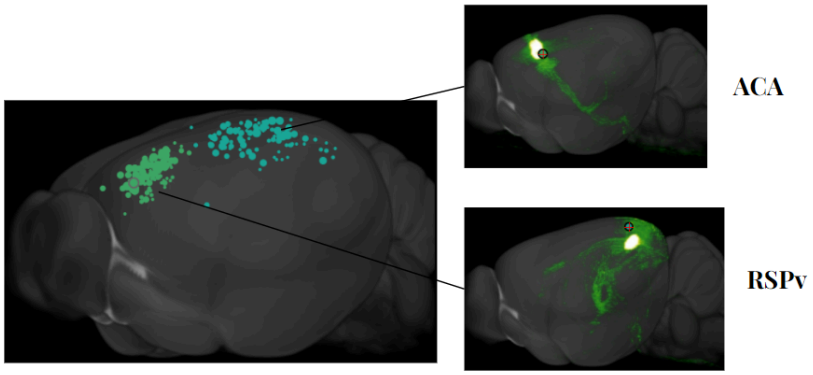
area (RSP) as well as the the Anterior Cingulate Area (ACA) are brain regions encompassed in the DMN that are affected by the Alzheimer's disease.



(Allen Brain Atlas)

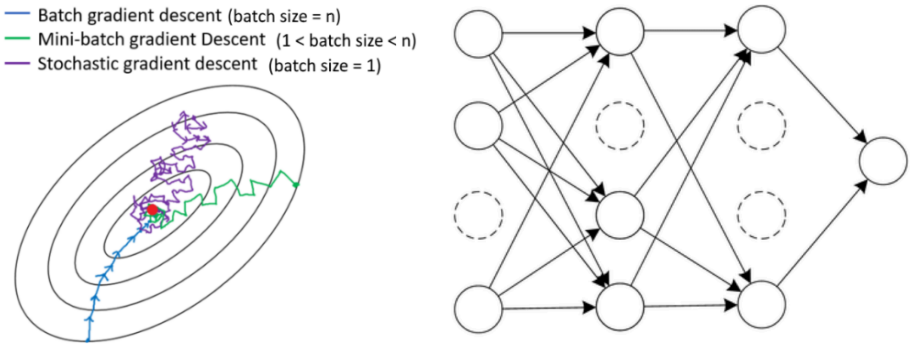
These brain regions can be studied using viral tracers through data provided in the Allen Brain Atlas. Viral tracers containing Green Fluorescent Protein appear well under two-photon micrographs, and serve to map the connections originating from the ACA and RSPv, which provide the basis for research in these areas. The effect of the Alzheimer's disease, a neurological disease that causes conditions like dementia and is characterized by the accumulation of the β-amyloid peptide (Aβ) in the brain along with the hyperphosphorylated and cleaved forms of the microtubule proteine tau. Research in genetics, biochemistry, and behavioral science suggest that physiologic generation of the neurotoxic β-amyloid peptide (Aβ) from sequential amyloid precursor protein (APP) proteolysis is the crucial step in the development of AD. Specific function of APP is not sknows but most studies suggest that overexpression shows a positive effect on cell health and growth. This effect is epitomized in transgenic mice that overexpress wild-type APP and have enlarged neurons (Oh et al. 2009).

Essentially, proteolysis (deletion or breakdown of proteins) on the Amyloid precursor protein is performed to lead to the generation of the AB peptide, thus inducing AD within animals.



(Allen Brain Atlas)

We chose to use a convolutional neural network to classify images of these areas. We used this architecture specifically because the convolution operation can detect specific visual features—from simple elements like diagonal lines to complex features like a nerve pathway—in an image while using relatively fewer connections. We modified this architecture to optimize it for our dataset, which was constrained by the currently available data. We applied dropout and regularization, techniques to prevent our model from overfitting and being unable to generalize its classification to previously-unseen images. We were also constrained by computational resources, so we chose to use mini-batch gradient descent to speed up the training process.



(Dabbura)

Materials and Technology

To program the neural network, we utilized Jupyter Notebook and Google Colab, and we accessed and processed data from the Allen Brain Institute using the Allen Brain Atlas Software Development Kit, or AllenSDK. For our Python Libraries, we used Pytorch for our deep learning architecture, Pynrrd for downloading experiment volumes, Numpy for array format for volumes and images, and Matplotlib for visualizations.

Methods

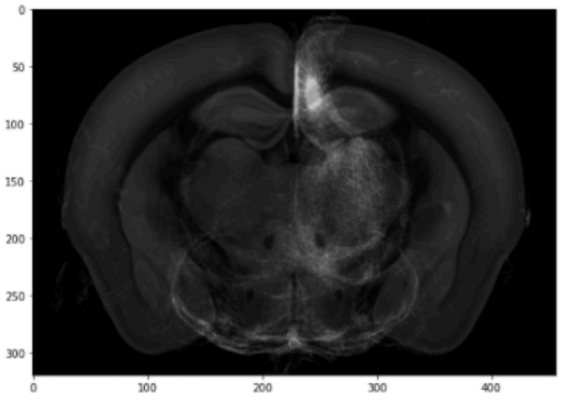
a. Data Collection

Using the Allen Mouse Connectivity Atlas, we downloaded projection volumes with dimensions 584x320x456 through the AllenSDK API. Projection volumes were generated in individual experiments at Allen Brain Institute by injecting viral fluorescent tracers into specific locations in Cre-line mice brains and visualized as 3D volumes with voxels through serial two-photon tomography. We downloaded projection volumes at a resolution of 25 micrometers. These volumes were converted to images by summing over the sagittal axis

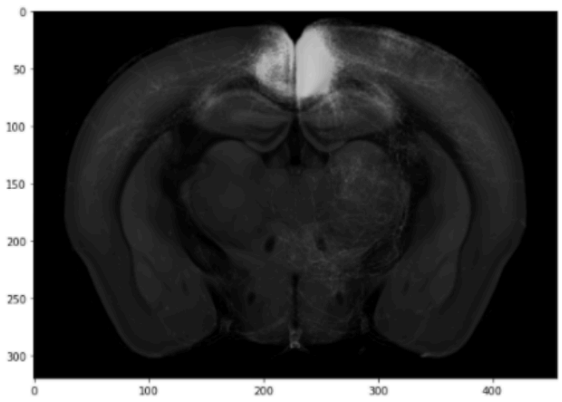
```
def collect_ids(*areas): # collecting projection volume experiments based
                         # on location, fluorescence volume
    experiment_ids=[]
    labels = []
    label = 0
    for area in areas:
        structure = structure_tree.get_structures_by_name([area])[0]
        experiments = mcc.get_experiments(cre=True, injection_structure_ids=[structure['id']])
        area_ids = []
        for exp in experiments:
            if exp['injection_volume']>0.05:
                area_ids.append(exp['id'])
                labels.append(label)
        experiment_ids += area_ids
        label += 1
    label_dict = dict(zip(range(label), areas))
    return experiment_ids, labels, label_dict
```

b. Experiment Selection

Each projection experiment is associated with a 9 digit experiment ID. We used the AllenSDK to filter experiments by the area in the brain in which the viral tracers were initially injected, or the injection location. We limited different parameters dependent on the classification task For the healthy brain analysis, we limited injections by the source injection location to either the ACA, or Anterior Cingulate Area, or the RSPv, or the ventral part of the Retrosplenial area For the cell types analysis, we limited injections by both the source location (ACAv, RSP, ENTm) and the cell type (PT, CT) based on the mice For the Alzheimer's analysis, we limited injections to ACAv in healthy and APP/PS1 mice Images were given a binary label depending on the analysis (labels represent We limited the amount of injections used by the injection volume, an indicator of visible fluorescence in a projection volume. Our threshold was 0.05 in order to ensure bright images.



One ACA experiment located in the brain (coronal view)

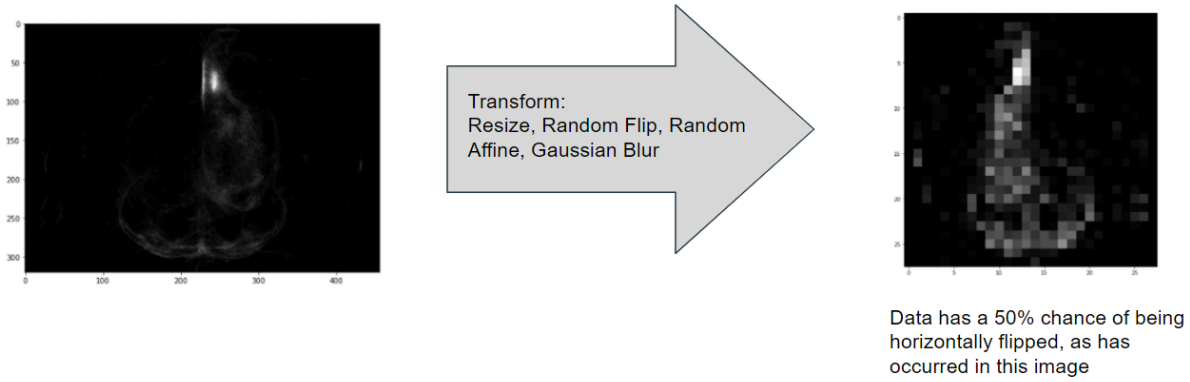


One RSPv experiment located in the brain (coronal view)

(Figure 1)

c. Resize Transformation

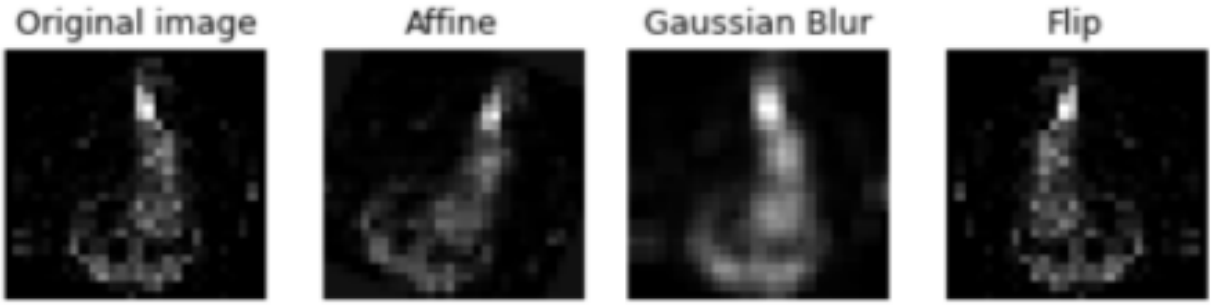
After creating summed slices for the experiments that matched our criteria, we transformed our images. See figure 2 for a visualization of the transformation pipeline for one sample image Resizing Limited by computational power, we chose to use 28x28 pixel images as inputs to our Convolutional Neural Network (CNN) This resolution matches the resolution of the classic MNIST dataset. We incorporated this resize in our transformation.



(Figure 2)

d. Augmentation

To increase the scope of the images our CNN could correctly classify, we applied random transforms to change some of the images in the dataset These transformations were: Gaussian Blur (sigma = 0.1) Horizontal Flip Affine (from 0 to 20 degrees)



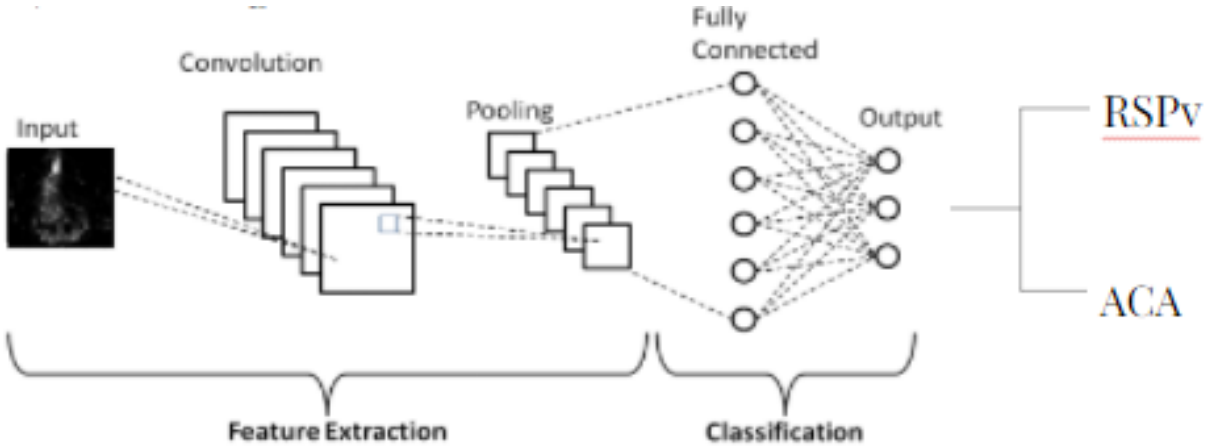
(Figure 3)

```
data_aug_transform = transforms.Compose([    # resizing and augmenting the images
    transforms.ToTensor(),
    transforms.Resize((28,28)),
    transforms.RandomApply([transforms.RandomAffine(degrees=(0, 20), interpolation=2, scale=(0.9, 1.1))
    transforms.RandomApply([transforms.GaussianBlur(kernel_size=3, sigma=0.1)], p=0.1),
    transforms.RandomHorizontalFlip(p=0.5),
    transforms.Normalize(mean=[.5], std=[.5])
])
```

(Figure 4)

e. Convolutional Neural Network Structure

Figures 3 and 4 show a code snippet and a visualization of the architecture of our CNN 3 Convolution operations extract features from the 28x28 input image. There are 3 fully connected layers at the end of the CNN with 400, 128, and 1 neurons.



(Figure 5)

```
def get_model():  # model architecture defined
  model = nn.Sequential(
      nn.Conv2d(1, 4, 3),
      nn.ReLU(),

      nn.Conv2d(4, 8, 3),
      nn.ReLU(),
      nn.MaxPool2d(2),

      nn.Conv2d(8, 16, 3),
      nn.ReLU(),
      nn.MaxPool2d(2),

      nn.Flatten(),
      nn.Linear(400, 128),
      nn.ReLU(),
      nn.Linear(128, 1), # BCE loss = sigmoid + CE
  )
  return model
```

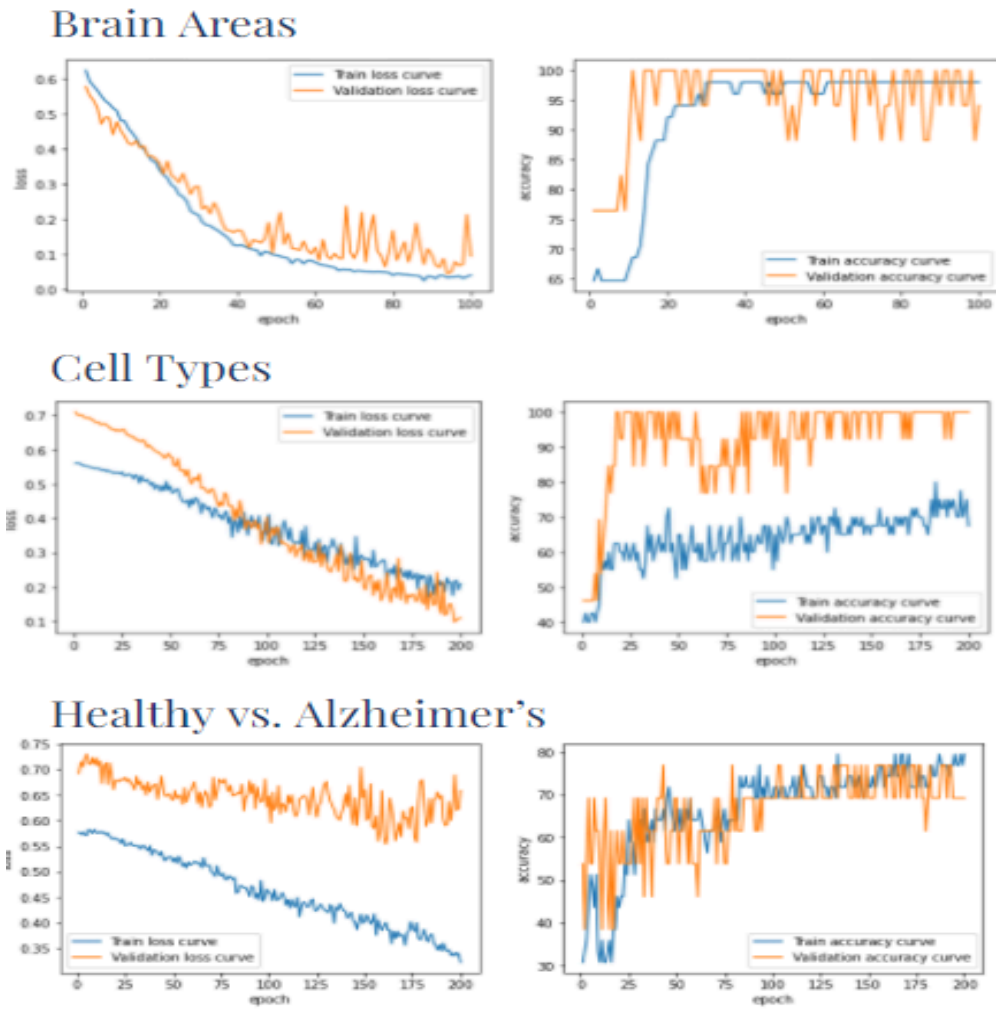
(Figure 6)

f. Model Hyperparameters for each network

Training/validation/test set breakdown was 51/17/18. The images in each set were randomly sampled. The training set determines model weights, the validation set further tunes these parameters, and the test set is used to assess model accuracy on foreign data Mini-batch Sizes. For training/validation/testing, 10/3/3 Images are fed to the model to update weights by mini-batches, or sets of data which concurrently update model weights during gradient descent. With that, the number of epochs (iterations of gradient descent) was 200, and the learning rate (proportion controlling the magnitude of changes to neuron weights) was 1e-4.

Results

For each area of our neural network, we had different accuracies For brain areas data, our training accuracy was 96.08% (51 images), our validation accuracy was 100.00% (17 images), and our test Accuracy was 94.44% (18 images). For Cell types, our training accuracy was 67.5% (51 images), validation accuracy 100.00% (17 images), our test accuracy was 92.86% (18 images). For the Healthy vs Alzheimer's data, our neural network had a training Accuracy of 66.67% (39 images), validation accuracy of 76.92% (13 images), and test accuracy of 85.71% (14 images).



Outcome and Discussion

We had 94% Accuracy for Healthy Brain Area Classification, 93% Accuracy for Cell Type Classification 86%, and the Accuracy for APP/PS1 Classification High accuracy demonstrates CNN effectiveness to quantify variability in the brain. The network can be extended to quantifying specific structural changes and multi-label classifiers can identify distinguishing features within one image Combining features can classify changes based on cell type and brain area to further elucidate disease progression.

Acknowledgments

We worked with the Georgia Tech Neural Data Science Lab, specifically Dr. Eva Dyer, Mehdi Azabou, and Ran Liu. We also utilized data and tools from the Allen Brain Institute.

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