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Quantifying the Impact of Type 2 Diabetes on Brain Perfusion Using Deep Neural Networks

Behrouz Saghafi[1], **Prabhat Garg**[1], **Benjamin C. Wagner**[1], **S. Carrie Smith**[2], **Jianzhao Xu**[2], **Ananth J. Madhuranthakam**[1], **Youngkyoo Jung**[2], **Jasmin Divers**[2], **Barry I. Freedman**[2], **Joseph A. Maldjian**[1], **Albert Montillo**[1]

[1]University of Texas Southwestern Medical Center, Dallas, TX, USA

[2]Wake Forest School of Medicine, Winston-Salem, NC, USA

Abstract

The effect of Type 2 Diabetes (T2D) on brain health is poorly understood. This study aims to quantify the association between T2D and perfusion in the brain. T2D is a very common metabolic disorder that can cause long term damage to the renal and cardiovascular systems. Previous research has discovered the shape, volume and white matter microstructures in the brain to be significantly impacted by T2D. We propose a fully-connected deep neural network to classify the regional Cerebral Blood Flow into low or high levels, given 16 clinical measures as predictors. The clinical measures include diabetes, renal, cardiovascular and demographics measures. Our model enables us to discover any nonlinear association which might exist between the input features and target. Moreover, our end-to-end architecture automatically learns the most relevant features and combines them without the need for applying a feature selection method. We achieved promising classification performance. Furthermore, in comparison with six (6) classical machine learning algorithms and six (6) alternative deep neural networks similarly tuned for the task, our proposed model outperformed all of them.

1 Introduction

More than 29 million people (9.3%) in the United States have diabetes [2]. In adults, Type 2 Diabetes (T2D) accounts for 95% of all diagnosed cases of diabetes. T2D is a metabolic disorder characterized by high blood sugar caused by insulin resistance or relative lack of insulin. It has been shown that prolonged T2D can result in chronic kidney disease (CKD), cardiovascular disease (CVD) and diabetic retinopathy. Since the brain consumes a disproportionately large amount of the body's energy relative to its overall mass, it is reasonable to suspect that diabetes may impact brain health. Currently the effect of T2D on brain health has been under-studied. Understanding these effects will help unravel this complex disease and enable a more comprehensive evaluation of candidate new therapies.

Albert.Montillo@utsouthwestern.edu.

Initial studies on T2D patients have found that diabetes [3,11] and renal [9,14] disease measures are associated with volumes of certain neuroanatomical structures, however the relationship between diabetes and the perfusion of the brain parenchyma has remained largely unknown. Additionally, according to the U.S. Center for Disease Control, African American adults are about twice as likely to be diagnosed with diabetes as European Americans [2]. Thus in this study we aim to identify the association between diabetes-related disease measures and regional brain perfusion in African Americans.

Several studies have linked diabetes to structural alterations in the brain. Sink et al. [14] found significant associations between renal measures and hippocampal white matter volume in African Americans with diabetic kidney disease, including the urine albumin to creatinine ratio (UACR) and the estimated glomerular filtration rate (GFR). Freedman et al. [3] reported an inverse association between aorta calcified plaque (a CVD measure) and the gray matter volume of hippocampus in African Americans with T2D. In a study using Diffusion Tensor Imaging (DTI), Hsu et al. [4] found that diabetes duration is significantly associated with white matter microstructure measures, such as mean diffusivity in several brain regions including bilateral cerebellum, temporal lobe, bilateral cingulate gyrus, pons, parahippocampal gyrus and right caudate.

Given that these studies have shown an association between diabetes and brain structure, we hypothesize that T2D also alters brain perfusion. This paper tests our hypothesis. Our main contributions are threefold. First, a massive univariate linear analysis approach is performed to identify candidate regions meeting the most stringent multiple comparisons correction criteria. Second, a fully-connected Deep Neural Network (DNN) architecture for predicting brain perfusion level is proposed which automatically learns optimal feature combinations and characterizes the T2D to perfusion association including any nonlinearities. Third, permutation testing is conducted to access the reliability of proposed model's accuracy via the notion of statistical significance.

2 Materials

This cross-sectional study consisted of 152 African Americans with T2D. Laboratory tests were conducted to acquire measures of diabetes as well as related renal and cardiovascular disease measures. The diabetes measures included hemoglobin A_{1c} (HbA_{1c}) and diabetes duration. Renal disease measures included UACR, GFR, blood urea nitrogen (BUN), serum potassium, total serum protein, and urine microalbumin. Blood based measures of cardiovascular disease and inflammation included calcified atherosclerotic plaque in the coronary arteries (CAC) and C-reactive protein (CRP). Demographic measures obtained included gender (56.8% female), age (mean 59.2 years), body mass index, smoking status, and hypertension. These measures are summarized in Table 1.

Anatomical and perfusion MRI were acquired for every subject using a 3.0 Tesla Siemens Skyra MRI (Siemens Healthcare, Erlangen, Germany) with a high-resolution 20-channel head/neck coil. T1-weighted anatomic images were acquired using a 3D volumetric magnetization-prepared rapid acquisition gradient echo sequence (Repetition time [TR]

2,300 ms; echo time [TE] 2.02 ms; inversion time [TI] 900 ms; flip angle [FA] 9°; 192 slices; voxel dimensions $0.97 \times 0.97 \times 1$ mm^3). Eight phase pseudo-Continuous Arterial Spin Labeling (pCASL) perfusion images were acquired with repetition time [TR] 4,000 ms; echo time [TE] 12 ms; inversion time [TI] 3000 ms; flip angle [FA] 90°; 26 slices/49 volumes; voxel dimensions $3.4 \times 3.4 \times 5$ mm^3.

3 Methods

Our overall pipeline consists of these steps: (1) derivation of the mean Cerebral Blood Flow (CBF) per brain region, (2) identification of candidate brain regions via statistical analysis, and (3) fitting a DNN to quantify the association between the candidate region's CBF and diabetes measures. Each step is detailed below.

3.1 Compute Mean Gray Matter CBF per Anatomical Region

CBF volumes were computed from pCASL perfusion images in native space. To parcellate the CBF maps into regional measures, each subject's pCASL volume was co-registered to the same subject's T1-weighted image using affine transformation. Then each subject's T1-weighted image was spatially normalized to Montreal Neurological Institute (MNI) space using a non-linear transform [1] computed using the VBM8 toolbox[1]. These transforms were combined to spatially normalize the CBF maps into MNI space. The automated anatomical labeling (AAL) atlas [15], implemented in WFU PickAtlas [7] was used to parcellate the CBF map into 116 anatomical regions. A gray matter mask from VBM8 segmentation was applied to limit to the gray matter CBF voxels. Finally, the mean gray matter CBF of the voxels in each region was computed to form a vector containing the 116 mean regional CBF measures.

3.2 Identify candidate regions for further analysis

At this point the data consisted of 16 diabetes related predictors and 116 candidate regional CBF target measures. To prune the list of candidate regions a massive univariate approach was applied to the 152 subject cohort. In this approach 116 multiple linear regression models, each defined as $y = b_0 + b_1 x_1 + b_2 x_2 + \ldots + b_{16} x_{16}$ was fitted, where y is one of the regional CBF measures and x_i are the clinical measures. For each model, the coefficient of determination or R^2 score was computed to measure the goodness of fit while the probability of F-statistic, p(F-statistic), was computed to measure the significance of the regression model. Bonferroni multiple comparisons correction was applied, yielding a criterion for significance of $\alpha = 0.01/116 = 0.000086$.

Figure 1 shows the regions, sorted based on decreasing R^2 from the linear model fit to each region. The p(F-statistic) is also shown. 17 structures pass the significance test, p(F-statistic) < 0.000086. The most significant region is the right caudate with p(F-statistic) = 1.16e − 07 and $R^2 = 0.36$. This agrees with the finding in [4] of an association between diabetes duration and mean diffusivity in right caudate, discussed in Sect. 1. This analysis reveals the

[1] http://dbm.neuro.uni-jena.de/vbm.html.

caudate as one of the structures significantly impacted by T2D, therefore in the following section we train a DNN to predict caudate CBF level from diabetes measures in order to quantify the association.

3.3 Estimate Candidate Region Association Using a DNN

Subjects were ranked based on the perfusion of the CBF in the right caudate, then the top 30% and bottom 30% samples were considered for classification. This resulted in 92 subjects: 46 with low and 46 with high CBF. Categorical features including education, sex, hypertension and amount of smoking were converted into numerical features. Each feature was scaled between zero and one. Several fully connected, DNN model architectures were evaluated to classify the caudate perfusion level. In each tested architecture, a strategy similar to the fully connected layers in AlexNet [6] and VGGNet [13], was chosen where the number of neurons is reduced in each successive hidden layer until the output layer. This allows a gradual build-up of a more and more abstract, high level features from lower level features. The rectified linear unit which is defined as $ReLU(z) = max(0, z)$ was applied as the activation function for each hidden layer neuron. A categorical output layer consisting of a single neuron per category was implemented via the softmax activation function defined as $S_j(z) = \frac{e^z j}{\sum_{k=1}^{2} e^z k}; \; j = 1, 2$. During training a batch size of 10 and learning rate of 0.001 was chosen based on empirical evidence. The ADAM optimization method [5] was used with $\beta_1 = 0.5$, $\beta_2 = 0.999$, and $\epsilon = 1e-08$ and weights were initialized to small random values near zero. In each validation test, early stopping with look ahead was employed, i.e. training was stopped when the network showed no improvement in validation accuracy for 15 epochs. To perform model selection, 72 subjects were randomly selected from the 92 to use as the training set while the remaining 20 subjects were held out as the test set and not used during model selection. Both training and test sets were balanced. The training set was further divided into training and validation via 5-fold cross-validation. The evaluated models and their average cross validation accuracy is shown in Table 2. These models include less deep architectures which underfit (model 16-8-2) and very deep architectures which overfit (model 16-16-8-8-8-4-4-4-2). The winning architecture and the DNN model that we propose is further illustrated in Fig. 2. The model contains 5 dense hidden layers, where 16 neurons were used in the first hidden layer, 8 neurons in the second and third and 4 neurons in the fourth and fifth layers. After selecting the proposed architecture, it was trained on the full training set and evaluated on the unseen held-out test set.

4 Results

4.1 Performance Comparison of the Learning Models

The proposed model achieves an accuracy of 90% with a sensitivity of 100% and specificity of 80%. Table 3 shows a comparison of the performance of the proposed model to widely used classical machine learning classifiers. The proposed DNN model outperforms the other algorithms in nearly all performance metrics. While the random forest had slightly higher specificity, it yielded inferior F1 score, AUC, accuracy, and sensitivity.

4.2 Statistical Significance of the Proposed Model

The null hypothesis was that the DNN cannot learn to predict the perfusion level based on the training set. The test statistic chosen was the accuracy on the unseen test set of 20 samples. The permutation testing procedure was as follows:

1. Repeat $R = 1000$ times:
    a. Randomly permute the N perfusion measures over the N diabetes feature vectors.
    b. Compute the value of the test statistic for the current permutation.
2. Construct an empirical probability distribution function (PDF) of the test statistic.
3. Compute the p-value of the test static without permutation.

The PDF for the accuracy test statistics are shown in Fig. 3. Upon evaluation the proposed model achieved statistically significant reliability; the probability of observing a classifier with higher accuracy than the proposed model is <1% ($p = 0.000999$). Thus with a significance level of $\alpha = 0.01$, we reject the null hypothesis in factor of the alternative hypothesis that the model has learned to predict the perfusion level with small expected error.

5 Discussion

Our study found the caudate to be the structure whose blood perfusion is most impacted by diabetes. This is a noteworthy finding because the caudate is a structure vital for optimum brain health. The caudate is located within the dorsal striatum of the basal ganglia, and is associated with motor processes as well as cognitive functions including procedural learning and associative learning [8]. It is also one of the structures comprising the reward system [16].

Previous studies [4,10,12,17] have shown that the structure of the caudate nucleus, particularly the right caudate is significantly impacted by T2D. Peng et al. [10] reported a significant reduction of gray matter volume in the caudate in patients with T2D compared to normal controls. A similar study in pediatric population [12] showed caudate nucleus volume was significantly reduced in T2D patients compared to non-diabetic controls. Zhang et al. [17] found an association between higher plasma glucose (common in diabetics) and the shape of the caudate. Moreover, Hsu et al. [4] discovered a significant association between diabetes duration and white matter microstructural properties such as mean diffusivity in several brain regions including the right caudate. These complementary studies that associate caudate structural changes with T2D, corroborate our finding that T2D impacts blood perfusion in the caudate nucleus.

6 Conclusions

In this paper, we quantify the association between T2D-related measures and brain perfusion. We propose a fully connected deep neural network to classify the perfusion in caudate into low and high categories based on 16 diabetes, renal, cardiovascular and demographic measures. The proposed model outperforms all the deep learning and classical machine learning models tested, achieves a classification accuracy of 90%, 100% sensitivity, and 80% specificity, and permutation testing shows the model to have statistically significant reliability.

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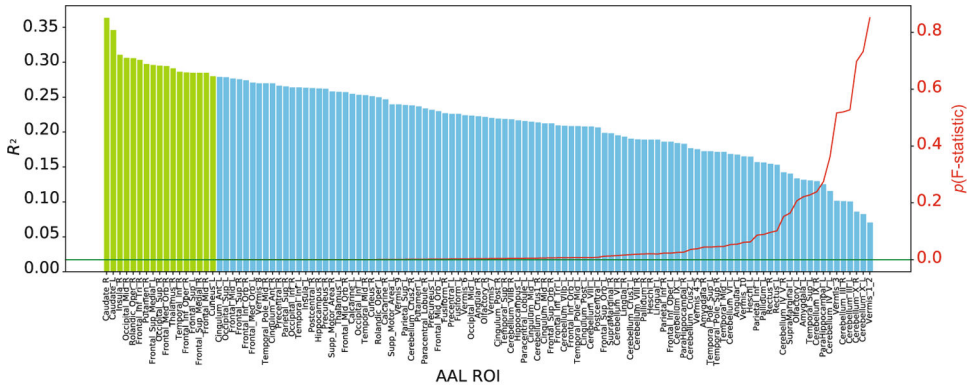

Fig. 1.

Fitting 116 multivariable univariate linear models for prediction of perfusion in each AAL ROI from the 16 clinical features. The structures are ranked based on the model's R^2. Also the p(F-statistic) is shown in red. The green horizontal line indicates the significance threshold based on Bonferroni correction which has a height of $\alpha = 0.000086$. The significant regions are highlighted in green.

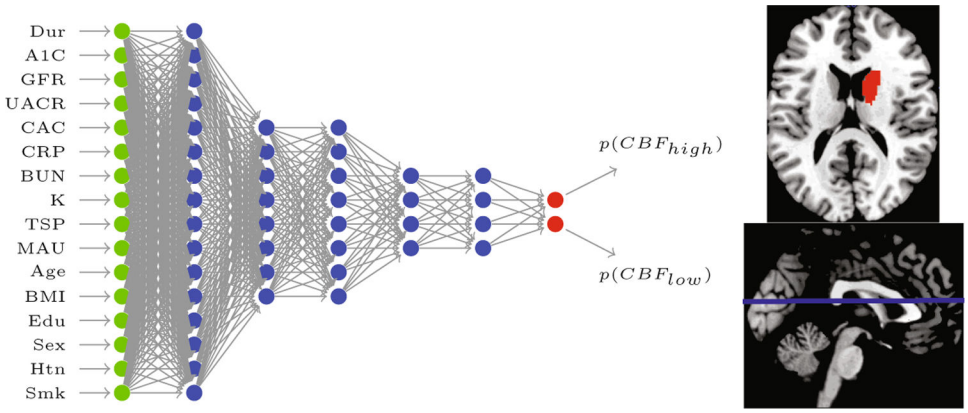

Fig. 2.

Our proposed fully-connected deep neural network for the classification of caudate CBF into perfusion level based on clinical measures. Green neurons represent the input layer, while blue neurons constitute the hidden layers and red neurons are the output neurons which use softmax activation function to compute a categorical distribution.

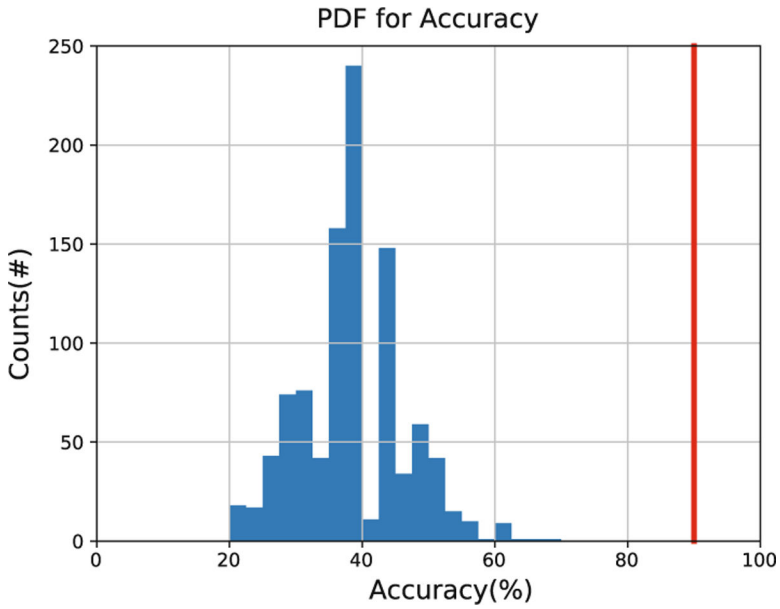

Fig. 3.

Probability distribution function (PDF) from permutation analysis for the proposed DNN model. The red line indicates the classification accuracy obtained by the model.

Table 1.

Diabetes and demographic measures included in the study.

Diabetes measures		**Demographic measures**	
UACR (mg/g)	83.7 (284.2)	Age (years)	59.2 (9.4)
CRP (mg/dL)	0.9 (1.5)	Female Sex (%)	56.8
HbA_{1c} (%)	8.0 (1.8)	Education (%)	
Diabetes duration (years)	8.9 (7.5)	Less than High School	9.0
CAC (mass score, mg)	475.4 (1142.2)	High school diploma	23.9
GFR (mL/min/1.73 m^2)	90.6 (23.5)	Some college	39.4
Serum Potassium (mmol/L)	4.1 (0.4)	Associate degree	7.7
Total Serum Protein (g/dL)	7.2 (0.5)	College graduate	11.6
BUN (mg/dL)	15.6 (5.8)	After college	8.4
Urine Microalbumin (mcg/mg creatinine)	110.2 (344.0)	BMI (kg/m^2)	34.1 (7.2)
		Smoking	
		Never (%)	52.3
		Past smoker (%)	28.8
		Current smoker (%)	18.9
		Hypertension (%)	86.4

Table 2.

Comparison of fully connected neural network architectures evaluated using 5-fold cross validation with 58 training subjects/fold and 14 test subjects/fold.

Model	5-fold cross-validation accuracy (%)
16-8-2	69.1 (±8.1)
16-16-8-2	75.9 (±14.9)
16-16-8-8-2	69.3 (±11.0)
16-16-8-8-4-2	74.8 (±8.9)
16-16-8-8-4-4-2	**76.3** (±9.9)
16-16-8-8-4-4-4-2	70.5 (±6.2)
16-16-8-8-8-4-4-4-2	65.0 (±9.7)

Table 3.

Comparison of the performance of different classifiers on the held out test set. Each model is trained on 72 subjects and tested on 20 subjects.

Classifier	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC (%)	F1-score (%)
proposed DNN	**90.0**	**100.0**	80.0	**90.0**	**90.9**
Linear-SVM	80.0	90.0	70.0	80.0	81.8
RBF-SVM	80.0	90.0	70.0	80.0	81.8
Extra Trees	80.0	90.0	70.0	80.0	81.8
Random Forest	85.0	80.0	**90.0**	85.0	84.2
Adaboost	80.0	90.0	70.0	80.0	81.8
Gradboost	70.0	80.0	60.0	70.0	72.7