Q-Net: A QUANTITATIVE SUSCEPTIBILITY MAPPING-BASED DEEP NEURAL NETWORK FOR DIFFERENTIAL DIAGNOSIS OF BRAIN IRON DEPOSITION IN HEMOCROMATOSIS

Soheil Zabihi†, Elahe Rahimian†, Sadaf Khademi†, Soumya Sharma†, Sean K. Sethi††, Sara Gharabaghi††, Amir Asif‡, E. Mark Haacke‡‡, Mandar S. Jog††, Arash Mohammadi††‡

†Electrical and Computer Engineering, Concordia University, Montreal, Canada
††Concordia Institute for Information Systems Engineering, Concordia University, Montreal, Canada
‡‡SpinTech MRI, Bingham Farms, MI, United States

ABSTRACT

Brain iron deposition, in particular deep gray matter nuclei, increases with advancing age. Hereditary Hemochromatosis (HH) is the most common inherited disorder of systemic iron excess in Europeans and recent studies claimed high brain iron accumulation in patient with Hemochromatosis. In this study, we focus on Artificial Intelligence (AI)-based differential diagnosis of brain iron deposition in HH via Quantitative Susceptibility Mapping (QSM), which is an established Magnetic Resonance Imaging (MRI) technique to study the distribution of iron in the brain. Our main objective is investigating potentials of AI-driven frameworks to accurately and efficiently differentiate individuals with Hemochromatosis from those of the Healthy Control (HC) group. More specifically, we developed the Q-Net framework, which is a data-driven model that processes information on iron deposition in the brain obtained from multi-echo gradient echo imaging data and anatomical information on T1-Weighted images of the brain. We illustrate that the Q-Net framework can assist in differentiating between someone with HH and HC of the same age, something that is not possible by just visualizing images. The study is performed based on a unique dataset that was collected from 52 subjects with HH and 47 HC. The Q-Net provides a differential diagnosis accuracy of 83.16% and 80.37% in the scan-level and image-level classification, respectively.

Index Terms— Hemochromatosis, Magnetic Resonance Imaging, Quantitative Susceptibility Mapping, Deep Neural Networks.

1. INTRODUCTION

Hereditary Hemochromatosis (HH) is an inherited disorder characterized by excessive iron absorption leading to organ iron deposition and is the most common autosomal recessive disorder in whites with a prevalence of 1 in 300 to 500 individuals [1–3]. Recent evidence suggests that brain iron deposition occurs in HH, in particular in the Deep Gray Matter (DGM) nuclei. In this study, we propose that an Artificial Intelligence (AI)-based model, which processes information on iron deposition in the brain obtained from multi-echo gradient echo imaging data and anatomical information on T1-Weighted (T1W) images of the brain, can accurately and efficiently differentiate individuals with HH from those of the Healthy Control (HC) group. In this context, we focus on Quantitative Susceptibility Mapping (QSM) [4, 5], which is an established Magnetic Resonance Imaging (MRI) technique to study the distribution of iron in the brain. QSM is obtained from phase information acquired using gradient echo imaging sequences representing the variations of the magnetic field, which occur as a consequence of an object’s magnetization within an external magnetic field [4]. Here, we focus on highlighting the differences between this work and previous relevant studies. On the one hand, Lee et al. [6] focused on classical Machine Learning (ML) methods such as Support Vector Machine (SVM) and Logistic Regression (LR) models, to differentiate between HCs and patients at the early stage of Parkinson Disease (PD). The accuracy of their optimal SVM and LR models on a dataset collected from 52 individuals were 79% and 73%, respectively. One main drawback of this approach is utilizing manually segmented ROIs such as the basal ganglia, for feature extraction. This is a time-consuming approach and requires clinical expertise. Moreover, hand-crafted and pre-defined features are constructed by simply using the mean QSM values of the segmented areas in the deep gray matter. This, in turn, results in the interpretation of high dimensional QSM scans with only seven numbers, which means that important textural and special information is ignored. Deep learning (DL), as an advanced ML technique, allows researchers to model non-linear decision surfaces through investigating very high dimensional spaces such as MR images. The main strength of DL techniques is that they can learn “on their own”. Therefore, using DNN models as an expert adviser or even a decision-maker system about the patient offers promising new ways to improve healthcare services. Bin et al. [7] suggested a hybrid feature extraction method (hand-crafted and DL-based features) to differentiate individuals with PD from HCs, aiming to enhance the outcomes. First, they manually extracted ROIs of the Substantia Nigra (SN) region in the brain using QSM images. Then, these ROIs were utilized to extract hand-crafted radiomics features from the SN region. Along with this approach, the ROIs were used to crop the QSM images to get the patches containing the SN region of the brain. These patches were then used to train a Convolutional Neural Network (CNN)-based model. Finally, they combined these two types of features, i.e., hand-crafted radiomics features and CNN features, to perform the classification task. Two machine methods, i.e., LR and SVM, were employed to predict PD and HC.

In this work, we investigate brain iron deposition in Hemochromatosis. The hypothesis is that the amount of iron deposition in
the brain of individuals diagnosed with Hemochromatosis is different than the HCs. However, visually discerning these distinctions with the naked eye proves challenging given that images exhibit a notable similarity. Despite such similarities, we hypothesize that an advanced AI-based model can perform such differential analysis based on the distribution of iron deposition in the brain obtained from QSM and R2* sequences rather than mean values of susceptibility or R2*. The main objective of this study was to investigate and illustrate the potential of using Machine Learning (ML), in particular, Deep Neural Network (DNN) architectures, to perform this difficult and challenging classification task. More precisely, we aim to use the potential power of DNNs for end-to-end extraction of discriminative features to differentiate between HCs from HHS based on QSM, R2*, and T1W images. To the best of our knowledge, this is the first study that develops a DNN-based model to differentiate patients with HH from HCs based on QSM and R2* sequences. In summary, the paper makes the following key contributions:

- Assessing the potential of AI-based models for differentiating HCs from patients with HH through investigating iron deposition in the brain.
- Development of a novel data-driven architecture, the Q-Net, is developed and trained over a unique dataset of QSM, R2*, and T1W images. This dataset is collected from 99 individuals, i.e., 47 HCs and 52 HHS, for the purpose of studying iron deposition in the brain.
- The processing pipeline of the Q-Net is an image embedding network and a sequential modeling architecture, which together form a classification paradigm for differential diagnosis. This architecture trains on its own to examine the images for extraction of expressive features, i.e., without relying on manually segmented Region-of-Interests (ROIs). More specifically, the training procedure of the Q-Net consists of the following two stages: (i) Training an image embedding network, which is constructed based on CNNs for the purpose of dimensionality reduction of the MR images through extracting differentiating features, and; (ii) Training a Recurrent Neural Network (RNN) to accurately distinguish and classify MR images by modeling the sequential nature of the MR data.

2. THE Q-Net FRAMEWORK

2.1. Dataset

The utilized dataset was collected from a total of 52 subjects with HH and 47 HCs from a single tertiary referral centre between February 2019 to February 2020. The study was approved by the local Ethics committee of Health Sciences Research Ethics Board, Western University, London, Ontario (protocol number 111467). All experiments were conducted in accordance with the Declaration of Helsinki, as well as the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans in Canada. All participants gave written informed consent. Subjects with HH without liver disease were recruited from the outpatient Gastroenterology Clinic at the Movement Disorders Centre. HCs were age and sex-matched to subjects with HH and were recruited by means of flyers. A multiple echo, multiple flip angle set of gradient echo imaging data were collected. Using the Strategic Acquired Gradient Echo (STAGE) data, it was possible to create QSM, R2*, T1, and spin density maps [4, 5, 8]. More precisely, STAGE uses T1W (high FA) and proton density (low FA) data to provide multiple contrasts and quantitative maps. QSM and R2* are well-established and sensitive methods for quantifying iron in the brain, and therefore we used both of them as inputs for the model. In addition, we used T1W images as a source of information about the anatomical structure of the brain. All subjects were imaged using a 3T Voyager with a 32-channel head coil (Discovery MR750; GE Medical Systems, Milwaukee, Wisconsin). Images were collected with the following parameters using a spoiled multi-echo Gradient Recalled Echo sequence: TE1 = 5 ms, TE6 = 30 ms, ΔTE = 5 ms, TR = 36 ms, FOV = 220 mm × 220 mm, matrix size 366 × 366, and slice thickness is 2 mm. Images were interpolated to a display resolution 0.43 mm × 0.43 mm. R2* maps were generated using a previously established method [8]. While QSM data were reconstructed for each echo individually using an in-house algorithm (SMART v2.0, MRI Institute for Biomedical Research, Bingham Farms, MI, United States) with the following steps: (i) The Brain Extraction Tool (BET) [9] was used to isolate the brain tissue (threshold = 0.2, erode = 4 and island = 2000) using the 2nd echo where the signal intensity is highest. (ii) The 3D Phase Unwrapping Algorithm (3DSRNCP) [10] was applied to unwrap the original phase data. (iii) The Sophisticated Harmonic Artifact Reduction (SHARP) [11] was utilized to remove unwanted background fields (threshold = 0.05 and deconvolution kernel size = 6). (iv) A truncated k-space division (TKD) based inverse filtering technique (threshold = 0.1) with an iterative approach (iteration threshold = 0.1 and number of iterations = 4) was used to reconstruct the susceptibility map [12]. (v) Finally, the result susceptibility map was constructed from the QSMs from T E2 − T E0 using a method which averages each TE based on its SNR [5].

2.2. Data Preparation

Q-Net Inputs: Currently in the medical imaging domain, QSM and R2* are the state-of-the-art methods to assess the regional iron concentrations. Both techniques reveal similar correlations with iron and are effective modalities for studying iron deposition. Consequently, for the design of the proposed Q-Net framework, we use these techniques to retrieve information about regional iron concentrations along with T1W images to account for information associated with the anatomical structure of the brain. More specifically, QSM, R2*, and T1W images are concatenated in a channel-wise fashion (resulting in a 3D input similar to RGB images) to be fed to the proposed Q-Net architecture. It is worth noting that, in this study, from the entire scans of each individual, we consider slices that include the basal ganglia region. In other words, based on the experts’ input, slices that include the basal ganglia region were selected and provided as input to the Q-Net.

Data Augmentation: Different data augmentation strategies are applied to the input images prior to being fed into the Q-Net network. Generally speaking, DNN models are data-hungry requiring a large number of input data for training purposes. Data augmentation is an effective and common strategy [13] to improve the performance of DNNs in scenarios where the training set is relatively small (which is a common situation in the medical domain and this study is not an
exception). There are several benefits associated with data augmentation among which is generating the extra samples in an effective and inexpensive manner. Moreover, it helps to the generalizability of the models by avoiding overfitting. More specifically, data augmentation helps the Q-Net learn the main concepts of the underlying problem, instead of memorizing the entire dataset, i.e., overfitting, which leads to a less efficient model. Our augmentation pipeline for training consists of the following methods: Histogram Stretching \((p = 1)\), Vertical Flip \((p = 0.5)\), Random Brightness and Contrast \((p = 0.7)\), Random Gamma \((p = 0.3)\), Grid Distortion \((p = 0.25)\), Shifting-Scaling-Rotating \((p = 0.5)\), and Cropping \((p = 1)\). The numbers in parentheses represent the probability of applying the corresponding augmentation method.

### 2.3. Internal Architecture of the Q-Net

Fig. 1 shows the architecture of the proposed DNN-based Q-Net model, which consists of two stages, i.e., Image-Level Modeling (referred to as Stage 1) and Scan-Level Modeling (referred to as Stage 2). In the Image-Level Model, ResNet18 is utilized as the backbone, which is followed by a Fully Connected (FC) layer [14]. ResNet18 is a Convolutional Neural Network (CNN) model composed of 18 layers. More specifically, the utilized ResNet18 architecture in this study starts with a \((7 \times 7)\) convolution layer followed by a Batch Normalization (BN) layer, Rectified Linear Unit (ReLU) activation function, and max-pooling layer. Then, it consists of 8 residual convolution blocks (ResBlocks) with the same structure. Each ResBlock contains two \((3 \times 3)\) convolution layers, each followed by a BN layer, while only the first convolution has a ReLU activation function. The input of each ResBlock is added to its output, this is why it is referred to as a Residual block. It is worth noting that we have down-sampling before the residual connection at 3rd, 5th, and 7th ResBlock, which are implemented by a \((1 \times 1)\) convolution layer with the stride of size 2 followed by a BN layer. Down-sampling layers double the feature maps’ dimension \((d)\) while reducing its specific dimensions, i.e., the width \((w)\) and height \((h)\), by a factor of 2. More specifically, the dimension of feature maps of the first convolution layer is 64, which increases to 128, 256, and 512 after each down-sampling. At the end, the final layers of the ResNet18 architecture are consist of a Global Average Pooling (GAP) layer followed by a FC layer. Although the GAP layer, similar to the max-pooling layer, is used to reduce the spatial dimensions of the feature maps, it performs an extreme type of dimensionality reduction, where feature maps’ tensor with dimension \(h \times w \times d\) are reduced in size to a lower-dimensional space of \(1 \times 1 \times d\). In other words, GAP layer reduces each \(h \times w\) feature map to a single number by simply taking the average of all \(h \times w\) values of that feature map.

The main purpose of the first stage is to build an image-level embedding network. To achieve this objective, the utilized ResNet18 architecture is initialized with ImageNet [15] weights, and the whole network was then trained based on the in-house dataset. As stated previously, QSM, R2*, and TiW, were concatenated in a channel-wise fashion and fed to Stage 1. The Stand-alone Image-Level Model cannot completely capture the underlying characteristics of input sequences as images from the same scan are considered completely independent from one another. Capitalizing on the fact that all images of the same scan/patient are potentially correlated, Stage 2, i.e., Scan-Level Model, was introduced to use and model inherit correlations among images of a patient. The Scan-Level Model utilized the trained embedding network of Stage 1 as an image feature extractor to feed a one-layer Bidirectional Long-Short Term Memory [16] (Bi-LSTM) network. The latter was utilized to combine the extracted features of the entire images of a patient. More specifically, we used the extracted features from each image after the GAP layer in the Image-Level Model’s architecture. Then, these features were used to train the Bi-LSTM layer. Intuitively speaking, the Bi-LSTM module integrates extracted features of all images of a patient.

Given \(X = [x^1, x^2, \ldots, x^t, \ldots, x^T]\) as an input sequence with length of \(T\), where \(x^t = [x_{1t}, x_{2t}, \ldots, x_{dt}]\) is a \(d\)-dimensional feature vector. The feature vector is extracted from input MRI sequence at position \(t\) representing the image index in the entire scan of an individual. The internal structure of an Long-Short Term Memory [17] (LSTM) cell is represented as follows

\[
\begin{align*}
\text{Input Gate: } i^t &= \sigma(W_i x^t + U_i h^{t-1} + b_i), \\
\text{Output Gate: } o^t &= \sigma(W_o x^t + U_o h^{t-1} + b_o), \\
\text{Forget Gate: } f^t &= \sigma(W_f x^t + U_f h^{t-1} + b_f), \\
\text{Cell State: } c^t &= f_t \odot c^{t-1} + i_t \odot \tanh(W_i x^t + U_i h^{t-1} + b_i), \\
\text{Cell Output: } h^t &= o_t \odot \tanh(c^t),
\end{align*}
\]

where term \(W_i, U_i, W_o, U_o, W_f, U_f, U_c\) represent weight matrices, and \(b_i, b_o, b_f\) represent the bias vectors. Furthermore, in Eqs. (1)-(5), \(h^t\) and \(c^t\) represent the hidden-state (also called cell-output) and cell-state of the LSTM, respectively. More specifically, the information flow of the LSTM’s internal cell structure is controlled by a gating logic consisting of three gates: (i) \(\text{Input Gate}\), which determines what information based on the input \(x^t\) and the previous hidden state \(h^{t-1}\) will be forwarded to the memory cell; (ii) \(\text{Output Gate}\), which controls the information that will be passed to the next hidden state \(h^t\); and, (iii) \(\text{Forget Gate}\) to determine the required information from the prior cell-state \(c^{t-1}\). Terms \(\sigma(\cdot)\) and \(\tanh(\cdot)\) denote the sigmoid and tangent hyperbolic activation functions, respectively; and operator “\(^t\)” denotes element-wise multiplication of two vectors. However, the LSTM cell can only capture previous context. To overcome this limitation, in Bi-LSTM architecture, 2 LSTMs are used in parallel to process the input in forward and backward directions. In other words, the input sequence is fed in normal time order for one network, and in the reverse time order for the other. Processing input in opposite directions increases the amount of available information for the model. In the proposed Q-Net model, the combined features, resulted from the Bi-LSTM module, were utilized by two independent FC layers to perform scan-level and image-level predictions.

### 2.4. Training Procedure

The training procedure of the Q-Net consists of the following two steps: (i) Training the Image-Level Model (Stage 1) to be used as an “Image embedding”, and; (ii) Training the Scan-Level Model (Stage 2) to perform scan-level and image-level predictions. In this context, the training step of Stage 1 is performed to generate an “Image embedding”, which can be seen as a function that takes a 3D input (channel-wise concatenated QSM, R2*, and TiW images) and returns a numeric vector as its representation. In other words, the image embedding translates/converts high-dimensional input images into numeric vectors in a lower-dimensional space. The embedding model, therefore, allows effective implementation of ML models on our large dimensional dataset by converting them into low-dimensional vectors. During the training phase of Stage 2 (scan-level modeling), image embedding from Stage 1 is used as a feature extractor to predict both image and scan-level labels. Image embedding is constructed by removing the FC layer from the architecture of Stage 1. It is worth noting that the embedding’s weights are not updated during the training phase of Stage 2. For training the architecture of both stages, cross-entropy loss is used. We used 10-fold
cross-validation for model training and evaluation. Specifically, we split the data on a patient basis for Stages 1 & 2, ensuring that the same patient’s images were included in the training set for both.

Learn an Image Embedding: For training an image embedding, we have to train an image-level classifier, i.e., identifying a given slice as belonging to a healthy or unhealthy category. For this purpose, we used ResNet18 [14] architecture as the backbone of the model, which is initialized with ImageNet [15] pre-trained weights. More specifically, we use the Transfer Learning (TL) technique to update the parameters of the model while the weights of the ResNet18 backbone are not frozen during the first training stage. Using TL has a considerable impact on performance improvement as the model leverages the capacity of DNN algorithms to learn discriminant features from large datasets. Moreover, during the training phase of the Image-Level Model, Stochastic Weight Averaging [18] (SWA) technique is applied to further improve the results. More specifically, SWA uses a modified learning rate schedule to compute an equal average of the weights traversed by Stochastic Gradient Decent (SGD). Utilization of the SWA technique can potentially improve the overall achievable performance compared to conventional training mechanisms [18]. For the first stage, the duration of training is 100 epochs with a batch size of 64, where Adam optimizer is used for model optimization. In first stage of the training, the learning rate starts from $3e^{-4}$ and declines to $1e^{-4}$ with cosine annealing [19].

Sequential Modeling: To account for potential correlations between consecutive QSM, $R_2^*$, and T1W images in an individual’s MRI series, RNN architectures (a class of DNNs for sequential modeling) is utilized within the Q-Net framework. However, due to the curse of dimensionality, direct use of images for training RNNs is computationally expensive, and it needs a large amount of data. To address these problems, we used our pre-trained image embedding network resulted from Image-Level Model. As shown in Fig. 1, for the embedding network, we use the Image-Level Model and remove its final FC layers. More specifically, we used the extracted features from each image after the GAP layer in Image-Level Model’s architecture. Then, the information of these extracted features, i.e., embedded images, are combined using Bi-LSTM layer. Therefore, with these considerations, the Scan-Level Model has the capacity of investigating the entire images of an individual’s scan, while considering their correlation leading to more accurate results. In the context of sequential modeling, we used the following two strategies: (i) Image-Level Classification, and; (ii) Scan-Level Classification.

In the first strategy, we classified each slice but unlike the training strategy used in Stage 1 (Image-Level Model), the information of slices in each scan are integrated by a Bi-LSTM layer, i.e., they are not considered as independent images. Then, a FC layer (shown as yellow blocks in Fig. 1) is leveraged to classify each slice. In the second strategy, i.e., the Scan-Level Classifier, the output features of the Bi-LSTM layer are concatenated and a FC layer is utilized to merge the information of all slices to predict the scan-level labels. The duration of training is 50 epochs with a batch size of 64, and the learning rate is fixed to $3e^{-4}$. It should be noted that the weights of the embedding network are frozen during this training stage.

3. RESULTS

3.1. Performance Evaluation based on Input Configuration

The following two scenarios are considered to evaluate the effects of different inputs on the performance of the proposed Q-Net: (i) The full-size image is utilized as the input of the model, and; (ii) Each image is cropped to fit the basal ganglia region, which is then used as the input to the model. In both scenarios, QSM, $R_2^*$, and T1W images are concatenated in a channel-wise fashion resulting in 3D inputs. In both scenarios, four different metrics, Accuracy, Sensitivity, Specificity, and F1-score, are utilized for performance evaluations.

As shown in Table 1, we have nearly equivalent accuracy and F1-score in all models for full-size image and cropped image inputs. Therefore, it could be said that we have nearly equal precision and recall, which is a piece of evidence that all models have the same performance in both classes, i.e., HC and HH prediction. In other words, models are not biased to predict a specific class more often than another. As shown in Table 1, by feeding cropped images to the models, we have an improvement in all criterion except Specificity. In other words, models are more capable to identify healthy individuals when full-size images are used as the input, which is also depicted in Fig. 2, where Q-Net with full-size image inputs occasionally score better in a specific region than Q-Net with cropped image inputs. However, in practice, the Q-Net with cropped image inputs have higher AUC (0.866) than Q-Net with full-size image inputs (0.851), which means it performs better in general.

3.2. Performance Evaluation from Modeling Perspective

In addition to considering two different input configurations, the performance of the proposed Q-Net framework is evaluated based on three different models, i.e., “ResNet”, “ResNetSWA”, and the proposed “Q-Net”. Please note that ResNetSWA model is similar in nature to the ResNet with the difference that the SWA technique [18] is leveraged during the training phase. As shown in Table 1, the performance of Q-Net is superior to that of ResNet and ResNetSWA models for image-level predictions. For example, Q-Net shows 7.28% and 5.17% accuracy improvement in comparison to ResNet.
Table 1. Results (MEAN ± STD) of the Image-Level classifiers for full-size and cropped image inputs.

| Input  | Metric       | Full Size Image | Cropped Image |
|--------|--------------|-----------------|---------------|
|        | Accuracy     | Sensitivity     | Specificity   | F1-score      | Accuracy     | Sensitivity | Specificity | F1-score      |
| ResNet | 68.19 ± 0.23 | 67.46 ± 1.24    | 69.00 ± 1.20  | 68.21 ± 0.26  | 68.46 ± 0.26 | 69.02 ± 1.28 | 67.16 ± 1.39 | 68.47 ± 0.29 |
| ResNetSWA | 70.36 ± 0.20 | 70.44 ± 0.39    | 70.26 ± 1.20  | 70.38 ± 0.21  | 71.17 ± 0.13 | 77.55 ± 0.12 | 64.06 ± 0.68 | 71.01 ± 0.14 |
| Q-Net  | 75.47 ± 0.80 | 70.36 ± 1.77    | 80.91 ± 1.54  | 75.43 ± 0.79  | 80.37 ± 0.70 | 82.43 ± 1.76 | 78.16 ± 1.14 | 80.35 ± 0.70 |

Table 2. Results of the Scan-Level classifiers for full-size and cropped image inputs.

| Input  | Metric       | Full Size Image | Cropped Image |
|--------|--------------|-----------------|---------------|
|        | Accuracy     | Sensitivity     | Specificity   | F1-score      | Accuracy     | Sensitivity | Specificity | F1-score      |
| ResNet | 75.79        | 75.78           | 77.55         | 73.91         | 76.84        | 76.83       | 77.55       | 76.07         |
| ResNetSWA | 76.89        | 76.84           | 80.43         | 73.46         | 81.05        | 80.77       | 81.83       | 79.56         |
| Q-Net  | 80.00        | 79.99           | 81.63         | 78.26         | 83.16        | 83.14       | 85.71       | 80.43         |

and ResNetSWA for full-size image inputs, respectively. Moreover, these accuracy improvements exceed to 11.91% and 9.2% for cropped image inputs, respectively. As shown in Table 1, the reported results of ResNetSWA are superior to those obtained from ResNet. For example, the accuracy is improved more than 2% in ResNetSWA model in comparison to ResNet in both full-size and cropped image inputs scenarios. This illustrates that the SWA technique can lead to a much better generalization. However, the results on the ResNet and ResNetSWA are achieved on the image-level, i.e., each image is considered entirely independent from other images of the same scan, which is a problem because, in practice, specialists consider entire scan of the patient for diagnosis. The proposed Q-Net addresses this issue by coupling a Bi-LSTM layer with the trained ResNetSWA as an image embedding module.

To summarize the performance of each classifier into a single criterion one common approach is to calculate the area under the ROC curve (abbreviated to AUC). For the full-size image inputs scenario, the AUCs of the ResNet, ResNetSWA, and Q-Net models are 0.747, 0.763, and 0.851, respectively. For the cropped image inputs scenario, AUCs of the ResNet, ResNetSWA, and Q-Net models are 0.749, 0.766, and 0.866, respectively. In both cases, Q-Net shows considerable improvement.

3.3. Scan-Level Classification

Table 2 shows the performance of the proposed Q-Net framework in scan-level classification based on full-size and cropped inputs configurations. As mentioned previously, ResNet and ResNetSWA are image-level classifiers. Therefore, in order to have scan-level predictions for these models, we used a voting mechanism. More specifically, the voting is performed as follows: Results from HC and HH predictions for all images corresponding to a patient are counted, and if the number of HC predicted images is more than HH, the patient is classified as an HC, and vice versa. On the contrary, in the Q-Net, we have a fusion module (FC layer) that combines all extracted features resulted from the Bi-LSTM layer to make decisions about the entire scan, as shown in Fig. 1. Reported results in Table 2 show that Q-Net model with cropped image inputs performs better than other approaches. For example, accuracy of ResNet, ResNetSWA, and Q-Net for full-size input images are 75.79%, 76.89%, and 80% respectively, while these are increased to 76.84%, 81.05%, and 83.16% for input images roughly cropped around the basal ganglia region. Moreover, in comparison to ResNet and ResNetSWA for full-size input images, Q-Net shows 4.21% and 3.11% accuracy improvements, respectively. For the cropped input images, on the other hand, improvements change to 6.23% and 2.11%, respectively. In comparison to ResNet and ResNetSWA, this improvement is achieved because of the Q-Net model’s specific characteristics, i.e., considering and integrating all images associ-
Table 3. DeLong test results for pairwise comparison of all ROC curves. If p-value is less than the pre-defined 5% (p < 0.05), the conclusion is that the two compared models are different. The significance of difference is categorized in multiple levels as follows: not-significant (ns): 0.05 < p ≤ 1; *: 0.01 < p ≤ 0.05; **: 0.001 < p ≤ 0.01; ***: 0.0001 < p ≤ 0.001; ****: p ≤ 0.0001.

| Input          | Model 1 | Model 2 | AUC 1 | AUC 2 | Difference STD Error | z-score | p-value | Sig. Level |
|---------------|---------|---------|-------|-------|----------------------|---------|---------|------------|
| Full Image Size | ResNetSWA | ResNet | 0.763 | 0.747 | 0.0083 | 1.928 | 0.0589 | ns         |
|               | Q-Net   | ResNet | 0.851 | 0.747 | 0.0087 | 11.954 | 6.2e-33 | ****       |
|               | Q-Net   | ResNetSWA | 0.851 | 0.763 | 0.0084 | 10.476 | 1.1e-25 | ****       |
| Cropped Image | ResNetSWA | ResNet | 0.766 | 0.749 | 0.0086 | 1.9767 | 0.0480 | *          |
|               | Q-Net   | ResNet | 0.866 | 0.749 | 0.0094 | 12.447 | 1.5e-35 | ****       |
|               | Q-Net   | ResNetSWA | 0.866 | 0.766 | 0.0089 | 11.236 | 2.7e-29 | ****       |

4. CONCLUSION

Brain iron deposition increases with age, making it very difficult to differentiate between individuals with an iron overload disorder (Hereditary Hemochromatosis) and healthy individuals. In this study, we applied an advanced AI model based on Quantitative Susceptibility Mapping, the Q-Net, to discover the potential relationship of the hemochromatosis with changes in brain iron content. We achieved accuracies of 83.16% and 80.37% in scan-level and image-level classification, respectively, through the analysis of an in-house high-dimensional MRI dataset. One of the primary limitations of our study is the small size of the dataset. Complex models such as Q-Net require substantial diverse training data to capture various patterns and nuances. With a larger and more varied dataset, the Q-Net model could leverage the additional information to enhance its performance, yielding more robust and accurate results. As part of our future plan, we aim to add more training data to improve the model’s efficacy. Moreover, we plan to study the contribution of each scan type, i.e., QSM, R2*, and T1W, to the final prediction to better understand their individual and combined impact on the model’s performance.

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