Age-Net: An MRI-Based Iterative Framework for Biological Age Estimation

Karim Armanious, Sherif Abdulatif, Wenbin Shi, Shashank Salian, Thomas Küstner, Daniel Weiskopf, Tobias Hepp, Sergios Gatidis, Bin Yang

Abstract—The concept of biological age (BA) - although important in clinical practice - is hard to grasp mainly due to lack of a clearly defined reference standard. For specific applications, especially in pediatrics, medical image data are used for BA estimation in a routine clinical context. Beyond this young age group, BA estimation is restricted to whole-body assessment using non-imaging indicators such as blood biomarkers, genetic and cellular data. However, various organ systems may exhibit different aging characteristics due to lifestyle and genetic factors. Thus, a whole-body assessment of the BA does not reflect the deviations of aging behavior between organs. To this end, we propose a new imaging-based framework for organ-specific BA estimation. As a first step, we introduce a chronological age (CA) estimation framework using deep convolutional neural networks (Age-Net). We quantitatively assess the performance of this framework in comparison to existing CA estimation approaches. Furthermore, we expand upon Age-Net with a novel iterative data-cleaning algorithm to segregate atypical-aging patients (BA $\neq$ CA) from the given population. In this manner, we hypothesize that the remaining population should approximate the true BA behaviour. For this initial study, we apply the proposed methodology on a brain magnetic resonance image (MRI) dataset containing healthy individuals as well as Alzheimer’s patients with different dementia ratings. We demonstrate the correlation between the predicted BAs and the expected cognitive deterioration in Alzheimers patients. A statistical and visualization-based analysis has provided evidence regarding the potential and current challenges of the proposed methodology.

Index Terms—Biological age estimation, deep learning, chronological age, magnetic resonance imaging.

I. INTRODUCTION

AGE is one of the most important parameters describing individuals in a medical context. For instance, age has a significant impact on the establishment of working diagnoses and the choice of appropriate diagnostic tests [2]. Similarly, age is also an important parameter influencing therapeutic decisions in a wide range of clinical situations [3], [4].

However, age-related biological phenotypes can deviate significantly between individuals within the same age group. These observations have motivated the concept of biological age (BA) in contrast to chronological age (CA) [5]. CA is described as the amount of time since the birth of an individual. Unlike CA, BA is not clearly defined. It can be described as a measure for the extent of genetic, metabolic and functional changes in an individual that occur during the process of aging. Thus, BA can be considered as an extension to the traditional concept of CA in addition to any organ-specific accelerated or delayed aging characteristics [6]–[8]. Despite this relatively imprecise definition, the potential impact of the concept of BA on patient management is easily conceivable. It is a common practice for clinicians to assess the overall condition of patients as part of the clinical examination relative to their respective age group and incorporate this impression into their medical decisions. However, these personal estimates are subjective and not easily quantifiable.

As an expansion to the concept of BA, the notion of organ-specific BA has been proposed aiming to describe changes in morphology, biology and function of organ systems that occur with aging [9]. This concept is based on the rationale that single organs or organ systems can be affected by different genetic or environmental factors and, thus, display different courses of aging. As an example, parameters of pulmonary function were proposed as measures for lung BA [10].

A large body of research attempts the quantification of BA using non-imaging data. More specifically, age-dependant variables such as genetic [5], [6], cellular [7], phenotypic [8], [11] and epidemiological data [12], blood biomarkers [13], [14] and physical activity [15] have been used as indicators for the BA. Traditional approaches rely on classical techniques such as multiple linear regression (MLR) [16] or the Klemara and Doubal (KD) method [17], whereas recent works adopt deep neural networks [18], [19]. The majority of these approaches utilize large cohort datasets for the prediction of the mortality risk [20]–[22]. Other methods incorporate CA as ground-truth labels and examine the relation between the predicted ages and other health indicators, such as the work ability index (WAI) [23] and frailty index (FI) [24], for assessing BA.

Nonetheless, the above non-imaging approaches lead to a whole-body assessment of BA. In that sense, they are not capable of recognizing the differences in aging characteristics between individual organ systems. In this context, medical imaging may potentially provide significant information al-
(a) Hybrid 3D network model with a stem network followed by a basic building block of two inception blocks and a fire module.

(b) Inception block basic architecture.

(c) Fire module basic architecture.

Fig. 1: An overview of the proposed chronological age estimation network (Age-Net) with the detailed architecture of each block. The network takes as an input either the whole organ volume or volume chunks of segmented brain gray matter (GM). The dimensions of the separate blocks are the same regardless the feeding strategy (full/chunks).

...allowing for non-invasive estimation of organ-specific BA.

The use of medical imaging for age estimation in a clinical setting is limited mainly to skeletal age estimation in infants and adolescents using conventional radiography and MRI [25]–[28]. Beyond skeletal age estimation, first studies have introduced the concept of brain age based on changes in brain morphology (e.g., changes in subvolumes) and provided evidence for associations between premature brain aging and cognitive function [29], [30]. Brain age can be defined by comparing an individual's morphological brain features to a reference data base of the underlying population. This is possible using brain MRI due to the highly constant anatomy of the central nervous system that allows for detection of age-dependent morphological deviations. Similarly, Alzheimer's disease was found to correlate directly with abnormal brain aging [31].

More recent efforts have incorporated the use of machine learning (ML) and deep learning (DL) techniques for medical imaging-based age estimation. Traditional approaches, such as kernel methods [32] and support vector machines (SVMs) [33], were initially utilized for brain CA estimation using T1-weighted MRI volumes. Also, atlas-based methods were employed to extract effective local features for the same task [34]. However, in recent years, the use of convolutional neural networks (CNNs) has become more prevalent due to strong results in a multitude of medical tasks, such as classification and segmentation [35]–[38]. For instance, a deep CNN has been utilized for prediction of brain age using 2D T1-weighted MR images [39]. This framework was then expanded upon to incorporate manually extracted features in addition to the 2D CNN architecture [40]. Recent advances have attempted the use of relatively shallow 3D CNN architectures to incorporate the spatial information between slices in the brain age estimation procedure [41], [42]. For forensic applications, a large body of research has utilized hand and skeletal MRI volumes to estimate the BA [42]–[45].

As stated clearly in the most recent survey on this topic [46], all DL approaches, whether imaging or non-imaging based, rely on the CA as ground-truth labels for BA prediction [41], [47]. Thus, the predicted ages cannot be used to assess the true aging characteristics of the test subjects. To the best of our knowledge, the problem of defining BA ground-truth labels is still not possible and remains an open research question.

The purpose of this study is to bridge the gap between chronological and biological age estimation. This is achieved by, first, introducing a new DL framework for organ-specific CA estimation using 3D medical imaging data. The performance of this framework is validated by a quantitative comparison with other concurrent CA estimation networks for brain age estimation. Additionally, a novel iterative training strategy is presented as an initial solution for approximating organ-specific BA labels. This is achieved by identifying outliers who exhibit atypical-aging characteristics. These outliers are then segregated from the training dataset. A serious challenge presents itself on how to validate the accuracy of the utilized training approach. To this end, we apply the proposed methodology on a dataset containing both healthy and Alzheimer's affected patients. Subsequently, we quantify the amount of...
Alzheimer’s patients detected as atypically-aging patients by the iterative strategy. Statistical and visual analysis of the results is conducted to illustrate the merit and limitations of the proposed methodology. This paper is organized as follows: Sec. II describes the proposed CA estimation network together with the conducted comparative study and the corresponding results. Sec. III presents the iterative data-cleaning strategy for BA estimation and describes the conducted experimental evaluations. Finally, Sec. IV presents the results and discussions for the BA framework followed by the conclusion in Sec. V.

II. CHRONOLOGICAL AGE ESTIMATION

In this section, the proposed DL architecture for organ-specific CA estimation is introduced. This network is later utilized as the foundation of the proposed iterative training strategy for BA estimation. A detailed description of the experiments conducted to validate the proposed architecture is presented.

A. Architectural Details

The proposed network for CA estimation, hereby referred to as Age-Net, is illustrated in Fig. 1. Based on an extensive assessment of different state-of-the-art DL structures, including ResNeXt [48] and DenseNets [49], among others, the proposed regression network was constructed out of a hybrid combination of inception v1 [50] and SqueezeNet [51] architectures.

The inception modules are based on the concept of split-transform-merge strategy where each module is comprised of parallel filters with different kernel dimensionality, which results in a network growing wider instead of deeper. This enables learning deeper feature representations by increasing the capacity of the network while mitigating the increased computation budget associated with network depth [50].

### TABLE I

| Layer                              | Output shape | # Parameters |
|------------------------------------|--------------|--------------|
| Input (Brain 3D chunk)             | 121 × 145 × 12 × 1 | —            |
| Inception stem network             | 16 × 19 × 12 × 192 | 445k         |
| Inception block - 3b               | 16 × 19 × 12 × 256 | 1.42M        |
| Inception block - 3c               | 16 × 19 × 12 × 480 | 3.18M        |
| Fire Module (α = 16, β = 64)      | 16 × 19 × 12 × 128 | 36.8k        |
| Inception block - 4b               | 8 × 10 × 12 × 512 | 5.33M        |
| Inception block - 4c               | 8 × 10 × 12 × 512 | 1.96M        |
| Fire Module (α = 16, β = 64)      | 8 × 10 × 12 × 128 | 36.8k        |
| Inception block - 4d               | 8 × 10 × 12 × 512 | 5.68M        |
| Inception block - 4e               | 8 × 10 × 12 × 528 | 6.04M        |
| Fire Module (α = 16, β = 64)      | 8 × 10 × 12 × 256 | 141k         |
| Inception block - 4f               | 4 × 5 × 6 × 832  | 9.70M        |
| Inception block - 5b               | 4 × 5 × 6 × 832  | 5.47M        |
| Fire Module (α = 32, β = 256)     | 4 × 5 × 6 × 512  | 524k         |
| Global average pooling             | 512           | —            |
| Dense layer 1                      | 512           | 260k         |
| Dense layer 2                      | 256           | 130k         |
| Dense layer 3                      | 128           | 32k          |
| Regression layer                   | 1             | 129          |
| # parameters (total)               | —             | 41M          |

For this work, we utilize the inflated inception v1 architecture, which is a 3D realization of conventional inception modules achieved via inflating all filters and pooling kernels into their 3D counterparts [52]. An illustration of an inflated inception module is illustrated in Fig. 1b.

Additionally, fire modules proposed in SqueezeNet are also incorporated in the Age-Net architecture [51]. They consist of squeeze-and-expand layers comprised of a combination of 1 × 1 × 1 and 3 × 3 × 3 convolutions that help reduce the total number of trainable parameters while enhancing the representation capacity. An illustration of the fire modules is depicted in Fig. 1c.

The final architecture for Age-Net is composed of an initial stem network consisting of 3 × 3 × 3 convolutions and max-pooling layers. This is followed by four modules concatenated together in an end-to-end manner. Each module consists of two inception blocks followed by a single fire module. In the above modules, each convolutional layer is followed by batch normalization and a ReLU activation function. L2 regularization is additionally utilized for each convolutional layer. A global average pooling layer is then applied as a structural regularizer to reduce the four-dimensional tensor to a one-dimensional output vector of 512 features. Finally, three dense layers combine additional gender information before a final regression layer outputs the predicted age. The complete architectural details of the Age-Net are outlined in Table I. Kernel parameters for the different inception blocks can be found in the original inception v1 publication [51].

B. Input Pipeline

Empirically, the method of feeding the input MR volumes to the Age-Net was found to have a significant impact on the network performance. Thus, two different approaches of feeding the 3D volumes are investigated in this work. First, entire MR volumes are fed as inputs to the network, which produces a single predicted age for each test subject. Due to the relatively limited number of training patients, data augmentation is essential to prevent network overfitting. Accordingly, horizontal flipping and translating the input volumes within...
Fig. 3: Examples of input brain GM from the axial orientation for (a) 23 year old subject, (b) 86 year old subject.

a pre-defined voxel-range \((30 \times 30)\) in the axial orientation were incorporated in the input pipeline. Despite its simplicity, this approach comes with a significant cost on the training efficiency due to the large memory space required as well as the on-the-fly data augmentations.

The second data feeding strategy entails dividing the input MR volumes into smaller 3D chunks and then feeding each chunk separately. This implicitly augments the training process by expanding the number of input samples to the network, thus, negating the need for on-the-fly data augmentations. The final predicted score for a test subject is then given as the mean of the predicted ages for the different input chunks. In addition to being advantageous from a training efficiency perspective, we hypothesize that this approach could assist in the unsupervised localization of anomalies and lesions per chunk. This can be achieved by investigating irregularities in the prediction scores for individual chunks compared to the CA ground-truth label for each test subject. However, this hypothesis will be further investigated in the future.

C. Dataset and Pre-processing

The proposed Age-Net architecture is evaluated on the task of estimating organ-specific CA for the brain region. For this purpose, we utilize the open source IXI dataset for brain MR scans \([53]\). T1-weighted MR scans with an original matrix size of \(256 \times 256 \times 150\) voxels from 562 subjects were utilized. The scans were acquired according to a flip angle of 8°, echo time of 4.6 ms and a repetition time of 9.8 ms. Scans from 420, 92 and 50 subjects were used for training, validation and testing, respectively. This was achieved while maintaining a balanced number of scans from all age-groups in all data subsets. For pre-processing, we utilize the steps recommended in \([54], [55]\). As a first step, all 3D volumes were realigned to provide a common orientation for brain visualization. This was achieved by utilizing the canonical Montreal Neurological Institute (MNI) 152 template adopted by the International Consortium for Brain Mapping (ICBM) \([54]\). Since the Gray Matter (GM) content of the brain was previously proven to be a strong indicator of the brain age \([56]\), the GM content of the aligned brain volumes was segmented using the statistical parameter mapping 12 (SPM12) software \([57]\). The resulting tissue maps were registered using DARTEL \([58]\) followed by normalization and modulation using a Jacobian deformation map. The resultant final GM volumes are of size \(121 \times 145 \times 121\) voxels. The CA histogram for the utilized brain MR volumes is depicted in Fig. 2 and example images are illustrated in Fig. 3.

D. Experiments

The proposed Age-Net architecture for CA estimation is investigated for the two different data feeding strategies described above. The first variant (Age-Net-volume) involves feeding the entire MR volume as input to the network. In contrast, the second variant (Age-Net-chunk) feeds smaller 3D chunks as inputs instead. Each volume is divided into 20 non-overlapping xx chunks of matrix size \(121 \times 145 \times 6\). Additionally, we hypothesize that including additional meta-information about the test subjects, i.e., gender, would assist in enhancing the age-regression performance. As such, an additional experiment was conducted to investigate the effect of including the gender (Age-Net-gender) with the chunk data feeding strategy.

To demonstrate the performance of Age-Net, quantitative comparisons were conducted against other regression networks previously proposed for brain MRI CA estimation. First, we compared against the framework provided in \([39]\) (2D-Huang) that consists of a modified deep VGG-Net \([60]\). Also, comparisons were conducted against a state-of-the-art brain age regression framework (3D-Ueda) \([59]\). This network is comprised of four 3D convolutional blocks together with max pooling and dense layers. All networks were trained until convergence to minimize the mean absolute error (MAE) loss function on a single NVIDIA Titan-X GPU using the Adam optimizer \([61]\) with Nesterov momentum (0.9) and a learning rate of \(10^{-4}\). All implementations of Age-Net will be made publicly available upon the publication of this work.\(^1\) Several metrics were calculated for the quantitative comparisons: the MAE, standard deviation (SD), bias, root mean square error (RMSE) and the correlation coefficient (Corr.) between the predicted ages and the ground-truth CA labels.

E. Results

The results of the CA estimation for the IXI brain dataset are presented in Table II and Fig. 4. The current approaches by Huang \([39]\) and Ueda \([59]\) exhibit comparable performance. The proposed 3D Age-Net architecture outperformed these two concurrent approaches across the utilized metrics. Feeding an entire MR volume as input enhanced the MAE to 2.66 years with a lower bias of 0.6 years and an improved RMSE of 3.58 years. Additionally, adapting the input pipeline to

\[^{1}\text{https://github.com/KarimArmanious}\]

| Model       | MAE   | SD    | Bias  | RMSE  | Corr. |
|-------------|-------|-------|-------|-------|-------|
| Age-Net-Volume | 2.658 | 3.532 | 0.608 | 3.584 | 0.979 |
| Age-Net-Chunk   | 2.283 | 3.546 | 0.902 | 3.659 | 0.978 |
| Age-Net-Gender   | 1.955 | 3.169 | 0.511 | 3.210 | 0.983 |

TABLE II
Quantitative comparison for CA estimation.
factors such as lifestyle and genetics. Thus, utilizing CA as aging is an organ-specific process affected by a multitude of approaches result in positive bias values. This indicates the tendency of the investigated test subjects to accommodate smaller 3D chunks instead of a full volume improved the MAE further by approximately 0.4 years albeit with an increased bias of 0.9 years. Furthermore, including the gender information with the chunk data feeding strategy resulted in the best quantitative scores represented by MAE of 1.96 years, the lowest systematic error of 0.51 years in bias and the smallest RMSE of 3.2 years. An interesting observation regarding the quantitative metrics is that all different CA estimation approaches result in positive bias values. This indicates the tendency of the investigated test subjects to exhibit accelerated aging characteristics.

III. BIOLOGICAL AGE ESTIMATION

The main challenge for image-based BA estimation is the lack of ground-truth labels since BA is not clearly defined \cite{18}. As such, previous approaches attempting this task had to, instead, rely on utilizing CA labels \cite{43}–\cite{45}. However, aging is an organ-specific process affected by a multitude of factors such as lifestyle and genetics. Thus, utilizing CA as ground-truth will not provide results that are indicative of the true aging features of the organs in question. Another option is to rely on subjective evaluations by radiologists. Nevertheless, this time-consuming and subjective process is challenging for large datasets and depends on the relative experience of the radiologists as it is not possible to accurately label the BA.

To resolve this challenge, we propose an iterative data-cleaning strategy to approximate BA labels. This is achieved by iteratively identifying and subsequently removing outliers that exhibit atypical-aging characteristics, whether accelerated (BA > CA) or delayed aging (BA < CA). The rationale behind this approach is to arrive at a typical-aging dataset in which the CA labels resemble the true BA labels (BA ≈ CA). We hypothesize that training on this dataset should help to bridge the gap from chronological to biological age estimation. Since the Age-Net-Gender framework was proven in the previous section to result in the best quantitative CA estimation, we hereby utilize this approach as the baseline for the following BA estimation approach. For simplicity, we hereby refer to this architecture as “Age-Net”. A basic outline of this strategy is depicted in Fig. 5. In the next sections, the introduced iterative data-cleaning strategy and the outlier detection procedure are further defined.

A. Iterative Data-Cleaning Strategy

A step-wise overview of the iterative data-cleaning strategy for BA estimation is illustrated in Fig. 6. Initially, the available brain MR scans were divided into training and testing datasets. Care was taken so that the training subjects represent the entirety of the available age spectrum in a balanced manner. For each iteration, the first step is to shuffle and split the training data into two subsets. The first subset is used to train an Age-Net architecture utilizing the chunk data feeding strategy with gender information (Age-Net-Gender) till convergence. This input pipeline was chosen as it showed the best results for CA estimation, as described above in Sec. II. The trained model is then validated on the second subset and the estimated CAs (CA) for the different patients is used to calculate a patient-dependent threshold γBA. This
threshold is then utilized for the detection of outliers who exhibit atypical-aging characteristics in the validation subset. The process of threshold calculation and outlier detection is explained in more details in the next subsection. The identified patients are then flagged as outliers. A new iteration would then be repeated starting with merging the validation samples with the training subset, reshuffling and repeating the process by training the Age-Net framework from scratch.

At the end of an iteration, if no outliers are detected in the validation subset, two arguments could be presented. First, the dataset has been thoroughly filtered out with all atypically-aging patients identified as outliers. Thus, no further refinement of the dataset is possible. Another explanation is that despite the lack of outliers in the validation data, some could still exist in the training subset. To protect against this possibility, an empirical stopping condition is enabled that states that three consecutive data-cleaning iterations trained with different initializations must yield no new outliers before the iterative strategy can be terminated.

Upon termination of the data-cleaning algorithm, all patients who were flagged as outliers in more than one iteration are removed from the training dataset. This serves to assert that no typically-aging patient is wrongfully detected as an outlier. Also, this process assists in maintaining the training data distribution during the data-cleaning strategy. Finally, an Age-Net architecture is trained on the cleaned dataset (after the removal of the outliers) where the CA labels should correspond approximately to the true BA labels (BA \( \approx \) CA).

**B. Outlier Detection**

In this work, we utilize a chunk data feeding strategy were each input MR volume is divided into \( K \) smaller chunks before being fed as input to the Age-Net. Outlier detection is initiated by first calculating a consolidated CA estimate for each patient in the validation dataset. This is achieved by averaging out the predicted ages (\( \hat{CA}_{n,i} \)) for each chunk \( i \) in the MR volume of patient \( n \) as:

\[
\hat{CA}_n = \frac{1}{K} \sum_{i=1}^{K} \hat{CA}_{n,i}
\]

Additionally, the standard deviation for the different chunk predictions is calculated for each patient as:

\[
\sigma_n = \sqrt{\frac{1}{K} \sum_{i=1}^{K} (\hat{CA}_{n,i} - \hat{CA}_n)^2}
\]

This is repeated for all patients to obtain the vectors:

\[
\hat{CA} = \begin{pmatrix} \hat{CA}_1 \\ \hat{CA}_2 \\ \vdots \\ \hat{CA}_N \end{pmatrix}, \quad \sigma = \begin{pmatrix} \sigma_1 \\ \sigma_2 \\ \vdots \\ \sigma_N \end{pmatrix}
\]

where \( N \) is the total number of patients in the validation dataset. For outlier detection, we compare the predicted age deviations (\( D \)) against a patient-dependent threshold (\( \gamma_{BA} \)), both defined as:

\[
D_n = |\hat{CA}_n - CA|, \quad \gamma_{BA,n} = R \cdot \sigma
\]

where \( R \) is a pre-defined constant value. The \( n^{th} \) patient is flagged as an outlier only if the age deviation exceeds the corresponding threshold value:

\[
D_n > \gamma_{BA,n}
\]

Assuming a normal distribution for the chunk predictions, the arbitrary constant \( R \) was set to 1.96 to reflect the 95% confidence interval of the mean predicted age of each patient, as illustrated in Fig. 7. At the end of each iteration, the training and validation datasets are reshuffled and a new iteration commences until the stopping condition is reached. Upon termination of the iterative data-cleaning, all patients detected as outliers are removed from the final training dataset only.
More specifically, we count the number of patients flagged as exhibiting atypical-aging characteristics. We apply this observation as an attempt to evaluate the capability of the iterative data-cleaning strategy in detecting atypically-aging individuals. We hypothesize that the proposed training strategy should be capable of accurately detecting patients with mild and moderate dementia as those theoretically exhibit the most pronounced atypical-aging characteristics.

Additionally, we compare the final predicted BAs, after applying the iterative data-cleaning framework, against the age estimates from an Age-Net trained by using CA as ground-truth labels. We illustrate, and subsequently analyze, the distributions of the resultant age estimates of the two frameworks. This was conducted separately for both cognitively healthy and Alzheimer’s patients.

Motivated by the recent interest in providing explainable DL frameworks, we attempt to shed light onto the reason beyond the predicted BA decision of our proposed network. For this purpose, we employ recent DL visualization techniques to highlight the most significant brain regions accounting to the network’s prediction from patients labelled as outliers or healthy by the iterative strategy. Specifically, we utilize at inference a combination of saliency-map visualizations [64], [65] together with GradCAM++ [66] for more finegrained visualization map. The resultant outputs of each visualization technique are combined via a product operation to obtain the final visualization maps. We compare the differences between the visualization maps from healthy and Alzheimer’s patients in the same age groups. Also, we analyze the visualizations of cognitively healthy individuals (CDR = 0) who were deemed by the framework as exhibiting atypical-aging characteristics, thus flagged as outliers by the proposed training strategy. Further, we analyze the percentage of cognitively healthy individuals (CDR = 0) and Alzheimer’s patients (CDR = 0.5, 1, 2) detected as outliers with respect to their corresponding populations in the training dataset. We hypothesize that the proposed training strategy should be capable of accurately detecting patients with mild and moderate dementia as those theoretically exhibit the most pronounced atypical-aging characteristics.

C. Dataset

Due to the lack of reference ground-truth BA labels, the validation of the proposed iterative data-cleaning strategy poses a key challenge. For this purpose, we investigate the performance of the introduced training strategy on a class-balanced subset from the OASIS-3 brain dataset [62]. This dataset encompasses T1-weighted MR scans from anonymized cognitively healthy individuals as well as patients suffering from dementia due to Alzheimer’s disease. The scans were acquired according to a flip angle of 10, echo time of 4 ms and a repetition time of 9.7 ms. The degree of cognitive deterioration in the Alzheimer’s patients is indicated by the clinical dementia rating (CDR), which distinguishes between questionable, mild and moderate dementia by the CDR scores of 0.5, 1 and 2, respectively [63].

In total, we utilize a subset of 1230 MRI scans from 950 patients in the age-range of 48-97 years. To ensure that the Age-Net is trained on a class-balanced dataset, we allocate 565 MR scans from 405 healthy patients and 185 scans from 165 Alzheimer’s patients for training the proposed framework. The remaining 490 scans from 380 patients (270: healthy, 110: Alzheimer’s) are assigned as the test set. The histogram of the utilized OASIS-3 data is depicted Fig. 8. The same preprocessing pipeline described previously in Sec. I-C was also applied with MR chunks of matrix size $121 \times 145 \times 6$ being fed to the framework as inputs.

D. Experiments

In previous studies, it has been reported that Alzheimer’s disease correlates directly with abnormal brain characteristics, particularly accelerated aging [31]. We apply this observation as an attempt to evaluate the capability of the iterative data-cleaning strategy in detecting atypically-aging individuals. More specifically, we count the number of patients flagged as outliers by the proposed training strategy. Further, we analyze the percentage of cognitively healthy individuals (CDR = 0) and Alzheimer’s patients (CDR = 0.5, 1, 2) detected as outliers with respect to their corresponding populations in the training dataset. We hypothesize that the proposed training strategy should be capable of accurately detecting patients with mild and moderate dementia as those theoretically exhibit the most pronounced atypical-aging characteristics.
IV. RESULTS AND DISCUSSION

The first step towards analyzing the proposed iterative data-cleaning strategy is to examine the detected outliers across consecutive iterations. As depicted in Fig. 9, a total of 18 training iterations were conducted before termination. This is due to satisfying the pre-defined stopping condition with no outliers detected in three successive iterations. Upon examining the population of patients with moderate dementia (CDR = 2), it is observed that the proposed strategy detects all aforementioned patients after 11 iterations. For Alzheimer’s patients with mild dementia (CDR = 0.5), 36 out of 49 patients were flagged as outliers in 16 iterations, amounting to a total of 73% of the CDR 1 training population. For questionable dementia (CDR = 0.5), 54% of this population were detected as outliers in 15 iterations. Conversely, for cognitively healthy individuals a substantially smaller percentage of patients (25%) were flagged as outliers. Compared to the number of outliers detected from Alzheimer’s patients, it is realistic for cognitively healthy individuals to less frequently exhibit atypically-aging characteristics. The above findings indicate that this training algorithm is capable of detecting atypical-aging characteristics whether Alzheimer’s-related or not. This demonstrates that the proposed training strategy is not only restricted to Alzheimer’s detection but reveals a higher generalizable potential. For instance, it can potentially be extended to different sources of brain deterioration such as tumours and lesions. Subsequently, all flagged outliers are removed from the training samples to create a typical-aging dataset (BA ≈ CA). Thereafter, an Age-Net framework is trained for the task of BA estimation using this filtered dataset.

Additionally, we also compare the predicted ages of the proposed BA estimation framework (after iterative data-cleaning) against those from a conventionally trained CA estimation Age-Net. The probability distribution functions (PDFs) of the deviations between the predicted ages and ground-truth CA labels for both frameworks are presented in Fig. 10. For the cognitively healthy population, minor perceivable differences can be observed in the distributions of both frameworks. This is illustrated in Fig. 10a with both of them adopting a normal distribution with a mean-deviation shift of 0.92 years. However, in Fig. 10b the predicted BA ages for Alzheimer’s patients manifest a substantially different behavior with a multimodal distribution as opposed to a normal distribution by the CA framework. Since Alzheimer’s disease was found to correspond with abnormal brain aging [31], it follows that the predicted BA scores for patients with dementia must exhibit a significant deviation from the corresponding CA labels. This desired behavior is signified in the proposed BA estimation framework with the majority of the predicted ages exhibiting an over-aging of approximately 8.2 years compared to the CA framework. We hypothesize that this reflects the capability of the proposed framework in recognizing true BA behavior. Also, a relatively smaller population of Alzheimer’s patients reveals under-aging behavior.

For the final set of experimental evaluations, we analyze the visualization maps from patients identified by the data-cleaning strategy as exhibiting atypical-aging characteristics. Thus, these patients were removed from the final BA training dataset. It is important to distinguish that these visualization maps reflects the network predictions rather than the actual brain voxel intensities. We also compare the resultant outlier visualization maps against those extracted from healthy individuals. As shown in Fig. 11, cognitively healthy individuals exhibit strong activations in the amygdala, hippocampus and thalamus in the axial plane as indicated by (○). This agrees with prior work investigating voxel-based morphometry of brain MRI of healthy patients [55]. In contrast, patients suffering from dementia (CDR > 0) identified as outliers manifest relatively weaker activations in the same regions, as indicated by (○). However, it is interesting to point out that cognitively healthy patients who were flagged as outliers (CDR = 0) reveal a noteworthy behavior. In some instances, the visualization maps from the aforementioned patients closely resemble the maps from dementia patients with similar highlighted regions of low intensity. For other outlier patients of CDR 0, the resultant visualization maps exhibit unconventional behavior with different highlighted regions of high intensity compared to cognitively healthy patients. For example, the regions in...
and around the fusiform gyrus depicts high activations in the outlier patients, as specified by ( ), in contrast to healthy individuals. On the whole, Alzheimer’s patients generally exhibit weakened networks activations compared to healthy individuals. Also, the CDR 0 outlier patients are either similar to dementia patients or display unique activations. We are of the opinion that the study of the activated brain regions for outliers could potentially prove to be beneficial for radiologists as it may assist in the early detection of disorders along with other various applications.

This initial study reveals the potential of utilizing MRI scans for BA estimation. The concept of incorporating an iterative training algorithm for approximating brain BA labels shows merit by detecting the majority of patients with moderate and mild dementia as outliers. This does not come at the expense of an overt detection of cognitively healthy patients as atypically-aging. Additionally, a visualization study highlighted the possibility of utilizing the proposed BA estimation framework to discover the deviation of seemingly healthy patients from their respective age groups.

As this study is among the first of its kind, our work has raised more questions than it has provided answers. Further clinical assessments by radiologists are necessary for the validation of the introduced framework. More specifically, a key question is the applicability of the BA framework on expanded MRI datasets from various organ systems with different disorders. This could be a step towards achieving an organ-specific BA assessment for patients using the whole-body MRI scans. This serves to evaluate the accelerated or delayed-aging characteristics of various organs within patients. The correlation between the deviations of the estimated BA scores and the presence of different disorders should be studied by radiologists together with the resultant visualization maps. Additionally, in the future, we plan to investigate the possibility of utilizing the BA visualization maps for anomaly detection of lesions and disorders in an unsupervised setting.

**V. CONCLUSION**

In this work, we present an initial study for organ-specific BA estimation using MRI scans. As an initial step, we develop a CA estimation framework capable of outperforming the current state-of-the-art MRI-based regression networks. Furthermore, we introduce a novel iterative training algorithm for excluding outlier patients exhibiting atypical-aging characteristics. This leads to the creation of a reference dataset where the available CA labels reflect the atypical-aging behavior. Upon validating the proposed BA framework on an Alzheimer’s dataset, the majority of patients with mild or moderate dementia were accurately detected as outliers. Moreover, the framework was found to be effective in detecting accelerated aging in Alzheimer’s patients in comparison to conventional CA estimation. Finally, an analysis was performed using established DL visualization techniques which reflects the potential of the introduced framework in discovering deviations of seemingly healthy patients from their respective age groups. In the future, we plan to expand the proposed framework via

![Fig. 11: Examples of the brain visualization maps for 3 axial chunks from healthy and outlier patients as detected by the proposed iterative strategy. Each column represents scans from a patient of the annotated CA value. The prominent activations in healthy patients were highlighted by ( ) whereas the corresponding activations in Alzheimer’s patients were labelled via ( ). Uncommon or unique activations detected in cognitively healthy outliers were labelled by ( ).](image)
the utilization of recent advances in Bayesian neural networks and uncertainty detection techniques to enhance the outlier detection procedure. Also, extension to different organ systems with whole-body MRI data would be investigated.

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