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研究課題名（和文）Development of Data-driven Prediction Model using 3D Multimodal Deep Neural Networks for Estimating the Evolution of White Matter Hyperintensities Associated with Small Vessel Disease in Brain MRI

研究課題名（英文）Development of Data-driven Prediction Model using 3D Multimodal Deep Neural Networks for Estimating the Evolution of White Matter Hyperintensities Associated with Small Vessel Disease in Brain MRI

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交付決定額（研究期間全体）：（直接経費）　　2,200,000円

研究成果の概要（和文）：White matter hyperintensities（WMH）とその老化がこの研究の焦点です。 WMHは、T2-FLAIR脳MRIに見られる神経放射線学的特徴であり、脳卒中および認知症に関連しています。 臨床研究によると、患者のWMHの量は、時間の経過とともに減少、同じまま、または増加する可能性があります。 ディープラーニングを使用して、WMHの進化と脳卒中病変のセグメンテーションの共同予測を実行することにより、WMHの進化の正確な予測モデルの開発に成功しました。 WMHの進化をより正確に予測することにより、医師は認知症の患者のための患者固有の治療法を作成することができます。

研究成果の学術的意義や社会的意義
In aging society like Japan, it is important for physicians to be able to predict the progression of neurodegenerative diseases such as dementia and Alzheimer's diseases. With our proposed model, physicians can perform patient specific treatment for dementia patient.

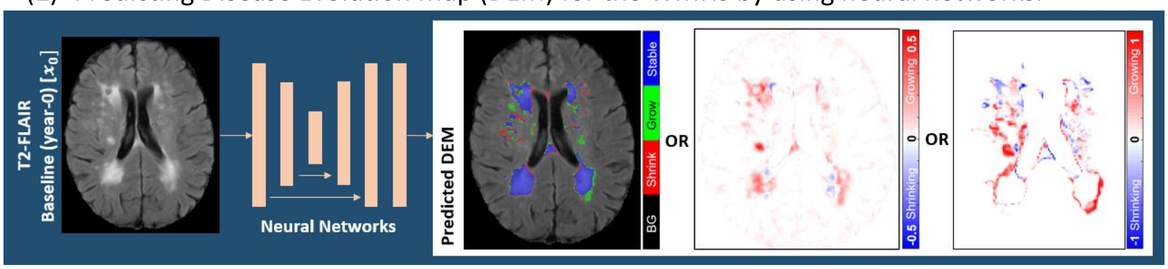
研究成果の概要（英文）：White matter hyperintensities (WMHs) and their evolution over time are the focus of this research. WMHs are neuroradiological features seen in T2-FLAIR brain MRI and associated with stroke and dementia. Clinical studies indicate that the volume of WMHs on a patient may decrease (i.e., regress), stay the same, or increase (i.e., progress) over time.

In this project, we successfully developed a more accurate predictive model for WMHs evolution using deep learning by performing joint prediction of WMHs evolution and stroke lesions segmentation. Furthermore, auxiliary input of stroke lesions probability maps also improved the performance of our model. These findings are important because (1) they confirmed previous clinical studies which elucidated that is as strong correlation between WMHs evolution and stroke lesions and (2) more accurate prediction of WMHs evolution can help physicians to create patient specific treatment for dementia patient.

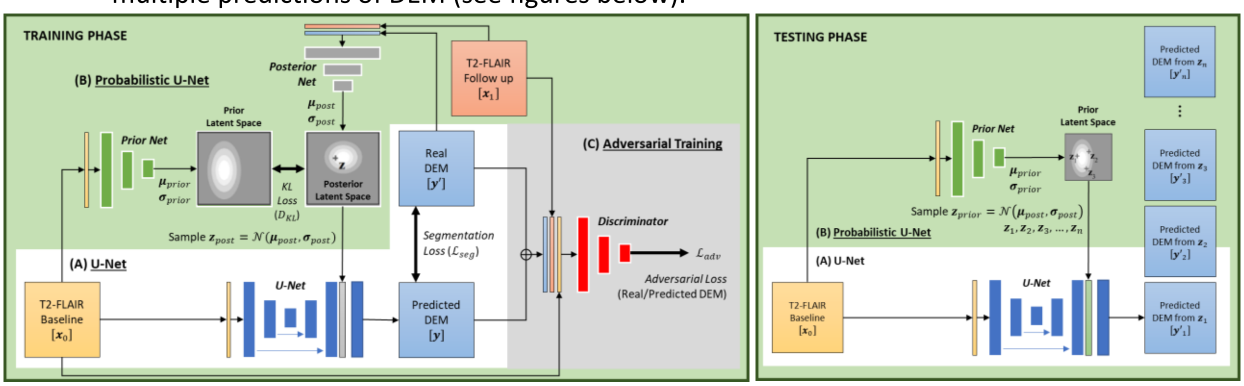
研究分野：Computer science

キーワード：White matter lesions　Progression of WMHs　Disease prediction model　Deep learning　Dementia　Alzheimer's disease

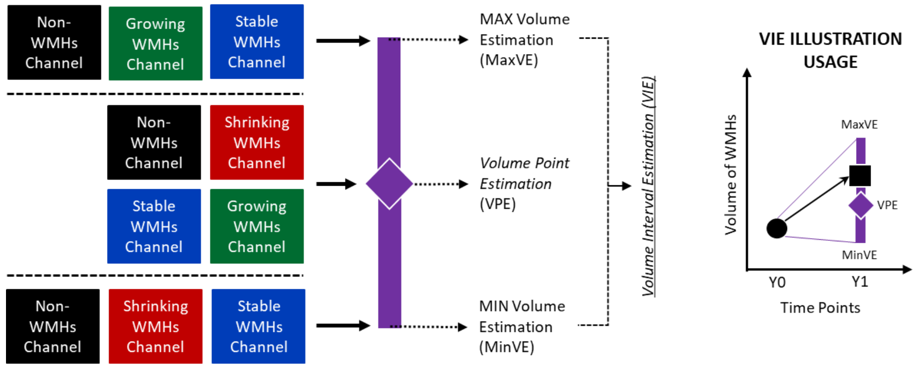
1. 研究開始当初の背景 (Background & Key Issues)
   (1) Previous studies have shown that the volume & shape of White Matter Hyperintensities (WMHs) on a patient may decrease, stay unchanged, or increase over time (i.e., evolution of WMH).
   (2) WMHs are associated with dementia, Alzheimer's Disease (AD), stroke, and multiple sclerosis (MS).
   (3) Predicting the evolution of WMHs is challenging because:
      ①. the rate of WMH evolution varies across studies and patients,
      ②. it involves a high degree of uncertainty, and
      ③. influencing clinical factors are poorly understood.
2. 研究の目的 (Main Objective)
   (1) Predicting Disease Evolution Map (DEM) for the WMHs by using neural networks.



3. 研究の方法 (Research Method)
   (1) Probabilistic U-Net with Adversarial Training was proposed to capture uncertainties in the prediction process of WMHs evolution. Unlike deterministic model, this model can produce multiple predictions of DEM (see figures below).



   (2) Volume Interval Estimation
   We argue that it is better to perform our proposed evaluation approach called **Volume Interval Estimation (VIE)**, where not only it estimates the future volume of WMHs (VPE), but also it estimates the minimum volume of future WMHs (MinVE) and the maximum volume of future WMHs (MaxVE). We do this by Dropping prediction channels of growing WMHs for MinVE and shrinking WMHs for MaxVE (see figures below)



4. 研究成果 (Results)

(1) U-Net vs. Probabilistic U-Net

Table 1 shows the performances of U-Net and Probabilistic U-Net for predicting the spatial progression of WMHs (shown in Dice Similarity Coefficient (DSC)) and in volume point estimation (VPE). Following the original paper that proposed the Probabilistic U-Net, we first used T2-FLAIR at first assessment (t0) and true DEM as inputs to Posterior Net. However, this approach was outperformed by the U-Net model. By, consequently, changing the input of Posterior Net to be T2-FLAIR at second assessment (t1) and true DEM, the model using Probabilistic U-Net outperformed U-Net in our experiments. These show that the input data for the Posterior Net in the Probabilistic U-Net should differ from the input data for the other modules of this probabilistic architecture (i.e., U-Net and Prior Net). Table 2 also shows that the Focal Loss (FL) cost function produced better prediction results than the weighted cross entropy (WCE) in both DSC and VPE for all experimental settings.

Table 1. Results for U-Net vs. Probabilistic U-Net

Model	Cost function	DSC ↑				VPE	
		Shrink	Grow	Stable	Average	Error → 0	MSE ↓
U-Net	WCE	0.1794 (0.072)	0.1970 (0.097)	0.6413 (0.159)	0.3393 (0.078)	−2.7127 (10.31)	112.87 (247.44)
	FL	0.1757 (0.077)	**0.2073 (0.104)**	0.6483 (0.156)	0.3438 (0.076)	−2.7002 (10.08)	108.17 (256.61)
Prob. U-Net (t0 & DEM as inputs to Posterior Net)	WCE	0.1491 (0.061)	0.1524 (0.090)	0.6220 (0.171)	0.3079 (0.086)	−2.5095 (9.84)	102.44 (234.61)
	FL	0.1673 (0.074)	0.1858 (0.089)	0.6147 (0.184)	0.3226 (0.090)	−2.0297 (9.27)	89.56 (220.73)
Prob. U-Net (t1 & DEM as inputs to Posterior Net)	WCE	0.1964 (0.071)	0.2040 (0.091)	**0.6564 (0.162)**	0.3522 (0.080)	**−0.2953 (8.33)**	69.05 (224.94)
	FL	**0.2092 (0.082)**	0.2056 (0.092)	0.6507 (0.160)	**0.3552 (0.080)**	−0.6650 (8.02)	**64.33 (220.39)**

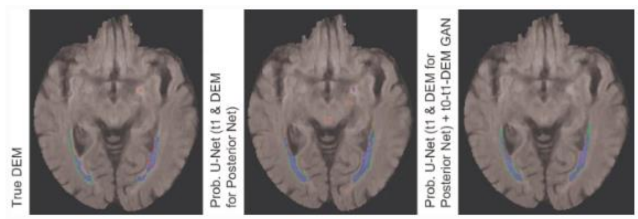
(2) Probabilistic U-Net with Adversarial Training

We investigated whether applying adversarial training with different input images can improve the performance of Probability U-Net. Table 2 shows that adversarial training with T2-FLAIR at t0 and true DEM slightly improved the prediction produced by Probabilistic U-Net in VPE (Error) and DSC (Stable).

Table 2. Results for Probabilistic U-Net with Adversarial Training

Model	DSC ↑				VPE	
	Shrink	Grow	Stable	Average	Error $\to 0$	MSE ↓
Prob. U-Net (t1 & DEM for Posterior Net)	**0.2092 (0.082)**	0.2056 (0.092)	0.6507 (0.160)	**0.3552 (0.080)**	−0.6650 (8.02)	**64.33 (220.39)**
Prob. U-Net (t1 & DEM for Posterior Net) + DEM GAN	0.1739 (0.083)	0.2083 (0.103)	0.6374 (0.172)	0.3399 (0.090)	2.0216 (9.32)	90.34 (180.32)
Prob. U-Net (t1 & DEM for Posterior Net) + t0-DEM GAN	0.1911 (0.093)	0.2184 (0.103)	**0.6530 (0.163)**	0.3541 (0.089)	**0.3155 (8.90)**	78.83 (156.17)
Prob. U-Net (t1 & DEM for Posterior Net) + t1-DEM GAN	0.1737 (0.083)	**0.2367 (0.100)**	0.6427 (0.169)	0.3511 (0.086)	−3.4385 (8.97)	91.70 (205.29)
Prob. U-Net (t1 & DEM for Posterior Net) + t0-t1-DEM GAN	0.1701 (0.083)	0.2282 (0.102)	0.6425 (0.167)	0.3469 (0.083)	-3.3115 (8.83)	88.36 (220.39)
U-Net	0.1757 (0.077)	0.2073 (0.104)	0.6483 (0.156)	0.3438 (0.076)	−2.7002 (10.08)	108.17 (256.61)
U-Net + t0-DEM GAN	0.1849 (0.091)	0.2134 (0.099)	0.6468 (0.159)	0.3484 (0.079)	−1.1187 (9.58)	92.44 (191.44)

Figure below also shows that the predicted DEM produced by adversarial training more closely followed the true DEM by removing the small false positive clusters in the prediction results. These experiments show that, while Probabilistic U-Net without adversarial training consistently produced some of the best prediction results in terms of DSC, the Probabilistic U-Net with adversarial training predicted more realistic DEM, closer to the true DEM, and with better VPE values. Additionally, U-Net with adversarial training produced better prediction results than the original U-Net without adversarial training.



Comparison of the true DEM (left) and predicted DEMs produced by using Probabilistic U-Net without adversarial training (middle) and Probabilistic U-Net with adversarial training with T2-FLAIR at t0 and true DEM (right).

(3) Volume Interval Estimation

Table 3. Results for Probabilistic U-Net by using Volume Interval Estimation

Model	CP ↑	CPinEVI ↑	(CP+WP) inEVI ↑	Distance to VPE (in *ml*)	
				MaxVE $\to 0$	MinVE $\to 0$
Prob. U-Net (t1 & DEM for Posterior Net)	**73.03**%	44.74%	51.32%	4.0862 (3.241)	−5.5700 (3.918)
Prob. U-Net (t1 & DEM for for Posterior Net) + DEM GAN	63.16%	30.26%	39.47%	2.5377 (3.0779)	−5.5978 (4.5046)
Prob. U-Net (t1 & DEM for for Posterior Net) + t0-DEM GAN	69.74%	39.47%	50.00%	2.6563 (3.0834)	−6.7103 (5.4319)
Prob. U-Net (t1 & DEM for for Posterior Net) + t1-DEM GAN	68.42%	44.74%	57.24%	2.8499 (2.7111)	−7.9550 (5.3201)
Prob. U-Net (t1 & DEM for for Posterior Net) + t0-t1-DEM GAN	**73.03**%	**48.68**%	57.89%	2.9383 (3.0793)	−7.6224 (5.5935)
U-Net	61.84%	36.84%	48.68%	2.9911 (3.3676)	-6.1355 (4.5706)
U-Net + t0-DEM GAN	72.37%	46.71%	**59.87**%	4.5915 (6.7208)	−6.2326 (4.7695)

Table 3 shows the performances of the deep learning models evaluated using VIE. The percentage of patients with correctly predicted DEM (i.e., subjects with shrinking and growing WMHs correctly predicted as having shrinking and growing WMHs respectively) is given by the metric called “CP” (Correctly Predicted). We also calculated the percentage of patients having their true future volumes of WMHs (Tt1V) correctly estimated and located between MinVE and MaxVE, and expresses it under a metric named “CPinEVI” (Correctly predicted in Estimated Volume Interval (EVI)). Lastly, “(CP+WP)inEVI” shows the percentage of correctly and wrongly predicted patients with their Tt1V still located between MinVE and MaxVE.

Both “CPinEVI” and “(CP+WP)inEVI” are important for better interpretation and higher confidence in our predictive model. Metric “CPinEVI” is important not only in evaluation but also in real-word testing/inference. A predictive model with higher rate of “CPinEVI” in testing means that there is a high probability that the Tt1V lies between the predicted/estimated MinVE and MaxVE produced by the predictive model. On the other hand, “(CP+WP)inEVI” captures difficult cases where the future volume of WMHs is wrongly predicted by the predictive model but the Tt1V still lies between the predicted/estimated MinVE and MaxVE. These cases happen mostly when the WMHs volume change from t0 to t1 is very small. For example, a patient with WMHs volume of 5 ml at t0 and 5.5 ml at t1 (i.e., growing WMHs) is wrongly predicted by the model to have future WMHs volume of 4.5 ml (i.e., shrinkage in the total WMHs volume at t1) while having predicted MinVE and MaxVE of 4 ml and 6 ml respectively.

The results in Table 3, show that Probability U-Net with adversarial training using T2-FLAIR for t0, t1, and true DEM produced the best results in all metrics of VIE. While the rate of CP is the same with the Probabilistic U-Net without adversarial training, Probabilistic U-Net with adversarial training using T2-FLAIR for t0, t1, and true DEM produced better results than other probabilistic models in “CPinEVI” and “(CP+WP)inEVI” (48.68% and 57.89% respectively). It is worth to mention that the best result for “(CP+WP)inEVI” was produced by the U-Net with adversarial training using T2-FLAIR for t0 and true DEM (i.e., 59.87% respectively). However, as shown in Table 2, it did not outperform any Probabilistic U-Net settings in DSC and/or VPE.

Lastly, one can argue that higher rates of “CPinEVI” and “(CP+WP)inEVI” can be produced by expanding the VIE itself (i.e., smaller value of MinVE and larger value of MaxVE). However, as shown in Table 3, the predicted values of MinVE and MaxVE from different predictive models are relatively close to the predicted VPE in all settings (calculated by performing MinVE - VPE and MaxVE - VPE for the whole dataset).

５．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計1件（うち招待講演　0件／うち国際学会　1件）

１．発表者名 Muhammad Febrian Rachmadi
２．発表標題 Probabilistic Deep Learning with Adversarial Training and Volume Interval Estimation - Better Ways to Perform and Evaluate Predictive Models for White Matter Hyperintensities Evolution
３．学会等名 PRIME 2021: Predictive Intelligence in Medicine（国際学会）
４．発表年 2021年～2022年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関