Diffusion Models for Contrast Harmonization of Magnetic Resonance Images

Abstract

Magnetic resonance (MR) images from multiple sources often show differences in image contrast related to acquisition settings or the used scanner type. For long-term studies, longitudinal comparability is essential but can be impaired by these contrast differences, leading to biased results when using automated evaluation tools. This study presents a diffusion model-based approach for contrast harmonization. We consider a paired data set originating from two different MR scanners, which produce images of different contrast due to scanner-inherent differences. We train a model to translate images from the source contrast, acquired with the first scanner, to the target contrast, as obtained with the second scanner. The aim is that the transformed scans display increased comparability with scans of the target contrast. As we only want to change the contrast, not the anatomical information, our method uses the original image to guide the image-to-image translation process by adding structural information. We use segmentations of cerebrospinal fluid, grey matter, and white matter to assess the increased comparability of transformed scans and scans of the target contrast.

Keywords: Diffusion models, contrast harmonization, image-to-image translation

1. Introduction

In medical studies using magnetic resonance (MR) images, data acquisition from multiple centers and different scanners is a common scenario, especially regarding comprehensive or long-term studies (Krüger et al., 2020). However, challenges arise when we compare data acquired with different MR scanners since the obtained MR images often display differences related to the acquisition settings and scanner variability (Dadar et al., 2020). For instance, as the magnetic field strength alters the level of contrast between different tissue types (Maubon et al., 1999; Ba-Ssalamah et al., 2003), the location of borders between different tissues can vary in images acquired with MR scanners of different field strength (Keihaninejad et al., 2010). Therefore, direct comparison of scans from different scanners with automated tools such as SIENA (Smith et al., 2002, 2004) is highly difficult. Consequently, a scanner change in the middle of a long-term study affects the automatic evaluation and longitudinal comparability of scans (Sinnecker et al., 2022). Longitudinal studies are important to monitor progressive diseases such as Multiple Sclerosis (MS), a demyelinating central nervous system disease (Mahad et al., 2015). It is essential that subsequent scans allow reliable interpretation of the disease progression without a bias related to a scanner change between the image acquisitions. In this work, we focus on a scanner change from 1.5 T to 3 T magnetic field strength that took place within a longitudinal MS study (Anonymous, 20xx). The goal of this work is to restore the comparability of the

Figure 1: Overview of our contrast harmonization method. We train a diffusion model using paired data from source contrast $\mathcal{S}$ and target contrast $\mathcal{T}$. We translate scan $B \in \mathcal{S}$ to scan $B_{transformed}$ that appears in contrast $\mathcal{T}$, allowing better comparability with $\hat{B} \in \mathcal{T}$.

images by mapping all images to the same target contrast. A paired data set was acquired by (Anonymous, 20xx) where healthy subjects and MS patients were scanned in the 1.5 T and the 3 T scanner within approximately 3.5 months. Due to the short time span between the acquisitions, we assume that the differences in the images of the same participant are only related to the different scanner types. We translate images from a source contrast $\mathcal{S}$ to a target contrast $\mathcal{T}$ by adapting a Denoising Diffusion Probabilistic Model (DDPM) (Ho et al., 2020; Wolleb et al., 2022b) for contrast harmonization. An overview is given in Figure 1, considering a pair $B \in \mathcal{S}$, $\hat{B} \in \mathcal{T}$ of the same subject. We translate scan $B \in \mathcal{S}$ to scan $B_{transformed}$ that appears in the contrast of $\mathcal{T}$. With cerebrospinal fluid (CSF), grey (GM) and white matter (WM) segmentations of the original and the generated images calculated using FAST (Zhang et al., 2001), we show that compared to the original B, $B_{transformed}$ presents better comparability with $\hat{B}$ from $\mathcal{T}$. Our code is available at https://anonymous.4open.science/r/DM_contrast_harmonization-8FFD.

Related Work Tracking brain volume changes over different scanners is prone to an error related to the scanner change (Lee et al., 2019). (Sinnecker et al., 2022) showed that given a paired data set, a corrective term for the volume computation can be calculated. To achieve a higher level of generalizability, images should be translated to the target contrast. DeepHarmony (Dewey et al., 2019), builds on the U-Net architecture (Ronneberger et al., 2015) and was developed for MR image contrast harmonization across protocol or scanner changes. For almost a decade, GANs (Goodfellow et al., 2014) have been the state of the art for image generation and image-to-image translation (Karras et al., 2021; Emami et al., 2020; Zhu et al., 2017; Isola et al., 2017). GANs such as (Dar et al., 2019; Liu et al., 2020; Luo et al., 2021; Peng et al., 2021) were created for multi-modal MR image synthesis, for instance T1 to T2-contrast. (Nie et al., 2017, 2018) performed cross-modal and cross-scanner image synthesis using GANs. Lately, DDPMs (Sohl-Dickstein et al., 2015; Ho et al., 2020) became the focus of attention. (Nichol and Dhariwal, 2021; Dhariwal and Nichol, 2021) further improved DDPMs, resulting in a transition of the state of the art for

image generation from GANs to diffusion models. Their application includes text-to-image generation as in (Rombach et al., 2022; Saharia et al., 2022b), image-to-image translation (Saharia et al., 2022a; Seo et al., 2022; Wolleb et al., 2022c), inpainting (Saharia et al., 2022a; Lugmayr et al., 2022; Wolleb et al., 2022c) and deformable image registration (Kim et al., 2022). The recently introduced diffusion models are also used in medical image analysis. For instance for cross-modal (Lyu and Wang, 2022) and multi-modal MR image synthesis (Özbey et al., 2022), anomaly detection (Wolleb et al., 2022a) and synthetic image generation (Pinaya et al., 2022). In medical studies, processing of three-dimensional (3D) data is often required. (Dorjsembe et al., 2022) showed the applicability of diffusion models to 3D data, but frequently, memory restrictions affect the processing of large volumes. In this paper, we generate consistent 3D volumes by stacking two-dimensional (2D) slices, allowing us to save memory during image-to-image translation.

2. Method

DDPMs as described in (Nichol and Dhariwal, 2021) form the basis for the proposed method. They are a class of generative models based on an iterative noising process q and denosing process p_θ. In the forward process q, Gaussian noise is added to an input image x for T time steps t. As the noise level is increased from a minimum at $t = 0$ to a maximum at $t = T$, each image $x_0, x_1, ..., x_T$ displays a higher amount of noise compared to the previous one. The forward noising process q is defined as

$$q(x_t|x_{t-1}) := \mathcal{N}(x_t; \sqrt{1 - \beta_t}x_{t-1}, \beta_t\mathbf{I}), \tag{1}$$

where $\mathbf{I}$ is the identity matrix and $\beta_1, ..., \beta_T$ are the forward process variances. With $\alpha_t := 1 - \beta_t$ and $\overline{\alpha}_t := \prod_{s=1}^{t} \alpha_s$ and using the reparametrization trick, x_t can be written as

$$x_t = \sqrt{\overline{\alpha}_t}x_0 + \sqrt{1 - \overline{\alpha}_t}\epsilon, \quad \text{with } \epsilon \sim \mathcal{N}(0, \mathbf{I}). \tag{2}$$

For the denoising process p_θ, the aim is to reverse the forward process, hence to predict x_{t-1} from x_t for $t \in \{T, ..., 1\}$. The learned model parameters θ define the reverse process

$$p_\theta(x_{t-1}|x_t) := \mathcal{N}(x_{t-1}; \mu_\theta(x_t, t), \Sigma_\theta(x_t, t)). \tag{3}$$

To map images of the source contrast $\mathcal{S}$ to the target contrast $\mathcal{T}$, we use the generative process of DDPMs. We adapt the method of (Wolleb et al., 2022b), originally created for DDPM-based image segmentation using paired data, to translate an image $B \in \mathcal{S}$ to $B_{transformed}$, which appears in the target contrast $\mathcal{T}$. The used data set provides for each of the m participants one corresponding 3D scan B of the source contrast $\mathcal{S}$ and one 3D scan $\hat{B}$ of the target contrast $\mathcal{T}$. Due to memory restrictions, we implement our model in 2D and slice each of the m scans of both contrasts into n slices and obtain for each participant $B = \{b_i\}_{i=1}^n$ and $\hat{B} = \{\hat{b}_i\}_{i=1}^n$ slices. We translate the slices $\{b_i\}_{i=1}^n$ originating from a scan $B \in \mathcal{S}$ such that they resemble the contrast of the slices $\{\hat{b}_i\}_{i=1}^n$ originating from $\hat{B} \in \mathcal{T}$, whereby each baseline slice b_i has its corresponding ground truth $\hat{b}_i$. During training, depicted in Figure 2, we pick a random timestep $t \in \{1, ..., T\}$ and apply Equation 2 with $x_0 = \hat{b}_i$ to compute a noisy image $x_{b_i,t}$ from $\hat{b}_i$. Since we only want to change the scanner-related image

Figure 2: Overview of the training. Anatomical information is given through the concatenation of image b_i from $B \in \mathcal{S}$ with noisy image $x_{b_i,t}$. X_t is used by the diffusion model to predict a slightly denoised image $x_{b_i,t-1}$ from $x_{b_i,t}$ using Equation 4.

contrast and not any anatomical features, we add anatomical information of our baseline image b_i through concatenation. We define the concatenated image as $X_t := b_i \oplus x_{b_i,t}$ which serves as input for our diffusion model. We can compute $x_{b_i,t-1}$ using Equation 4, which summarizes a denoising step as

$$x_{b_i,t-1} = \frac{1}{\sqrt{\alpha_t}} \left(x_{b_i,t} - \frac{1-\alpha_t}{\sqrt{1-\overline{\alpha_t}}} \epsilon_\theta(X_t,t) \right) + \sigma_t \mathbf{z}, \quad \text{with } \mathbf{z} \sim \mathcal{N}(0,\mathbf{I}), \quad (4)$$

whereby $\epsilon_\theta(X_t,t)$ is the output of the diffusion model at time step t, σ_t describes the variance scheme and $\mathbf{z}$ denotes the stochastic component of the process. The loss used to train the diffusion model ϵ_θ can be written as

$$|| \epsilon - \epsilon_\theta(X_t,t) ||^2 = || \epsilon - \epsilon_\theta(b_i \oplus (\sqrt{\overline{a_t}}\hat{b}_i + \sqrt{(1-\overline{a_t})}\epsilon),t) ||^2, \quad \text{with } \epsilon \sim \mathcal{N}(0,\mathbf{I}). \quad (5)$$

For the two directions of the transformation, 1.5 T to 3 T and 3 T to 1.5 T, two separate models need to be trained, as source and target contrast change. To translate a scan volume $B = \{b_i\}_{i=1}^n \in \mathcal{S}$ to the target contrast $\mathcal{T}$ during sampling, we translate every slice b_i to the synthetic slice $x_{b_i,0}$ in the contrast of $\mathcal{T}$. Figure 3 summarizes the sampling process starting from $x_{b_i,T} \sim \mathcal{N}(0,\mathbf{I})$. The previously trained denoising model is now applied for every denoising step $t \in \{T,...,1\}$ using Equation 4. Anatomical information is also added for every step t of the denoising process through the concatenation of b_i and $x_{b_i,t}$. We then stack the n output slices $x_{b_i,0}$ to create our final 3D output volume $B_{transformed} = \{x_{b_i,0}\}_{i=1}^n$, displaying the whole brain in target contrast.

3. Data Set and Training Details

We used a data set exclusively created to track a scanner change from a 1.5 T Siemens Magnetom Avanto to a 3 T Siemens Magnetom Skyra^{fit} whole-body scanner in 2016 (Anonymous, 20xx). Scanner details can be found in Appendix A. The participants' data is not public due to data privacy protection. Written consent was obtained from all participants. The data was coded (i.e., pseudoanonymized) at the time of the enrollment of the patients and includes scans of 22 healthy controls and 18 MS patients. All participants were scanned first in the 1.5 T scanner and after a median time interval of 3.5 months in the 3 T scanner.

Figure 3: Translation from $B \in \mathcal{S}$ to $B_{transformed}$. Each slice b_i of $B \in \mathcal{S}$ is iteratively denoised by applying Equation 4 for steps $t \in \{T, ..., 1\}$, whereby slice b_i is used to add anatomical information through concatenation. The 2D output slices $\{x_{b_i,0}\}_{i=1}^n$ get stacked to $B_{transformed}$, showing the input scan B translated to $\mathcal{T}$.

The relatively short time span between the scans ensures that no major disease progression happened in the MS patients, allowing a direct comparison of the scans and thereby forming a paired data set. Data set details can be found in Appendix B. Pre-processing of the original 3D data includes skull-stripping using HD-BET (Isensee et al., 2019), biasfield correction (Tustison et al., 2010), resampling of voxel spacing to $1 \times 1 \times 1$ mm^3 removal of the top and bottom 0.1 percentile of voxel intensities and normalization to voxel values between 0 and 1. With the ANTsPyx package, the paired images were registered based on affine and deformable transformation, using mutual information as similarity metric and an elastic regularization (Avants et al., 2014). We sliced each pre-prepocessed 3D scan into 160 sagittal slices of shape [246, 262] that were then cropped to a size of [224, 224]. The cropping only affected background pixels. We trained our models for 300,000 iterations with a batch size of four on a NVIDIA GeForce RTX 2080 Ti GPU, taking about 60 hours. As in (Wolleb et al., 2022b), the number of channels in the first layer of the model is 128, and one attention head is used at resolution 16, resulting in 11,402,370 model parameters. The learning rate used is 10^{-4} for the Adam optimizer. T is set as 1000. Details on hyperparameters and architecture can be found in (Nichol and Dhariwal, 2021). Training details of the comparing methods can be found in Appendix C. In addition to MSE calculation and histogram analysis, we evaluated CSF, GM and WM segmentations using FAST (Zhang et al., 2001) for the original images and the generated images. We did a four-fold cross-validation, combining data of healthy controls and MS patients in each fold. For each fold, the slices of 30 scans were used for training and those of 10 scans for testing.

4. Results and Discussion

For the evaluation, we compare our diffusion model (DM) with DeepHarmony (DH) (Dewey et al., 2019) and $pGAN$ (Dar et al., 2019). Each method takes an image $B \in \mathcal{S}$ from the test set and generates the image $B_{transformed}$ appearing in target contrast. The direct comparison of B versus $\hat{B}$ is denoted as *Original*. All tables in this chapter show the averages obtained over a four-fold cross-validation, the variance is listed in Appendix D.

Figure 4: An exemplary coronal slice of a scan $B \in \mathcal{S}$, the corresponding ground truth slice of $\hat{B} \in \mathcal{T}$ and slices of its transformations $B_{transformed}$ in contrast $\mathcal{T}$ generated by DH, $pGAN$ and our DM are shown for both translation directions. Further examples are in Appendix E.

Figure 4 contains examples of generated images and the corresponding input and ground truth slices. The original 1.5 T and 3 T images differ in contrast. While $pGAN$ and our DM generate convincing transformations of the input images to target contrast, DH blurs the image and increases the brightness excessively for both directions of the image mapping. The example images in Figure 4 are coronal slices from a 3D volume that was built by stacking sagittal slices. While images generated by $pGAN$ contain some stripe artefacts due to stacking in the border regions of the brain, our DM does not create any stripe artefacts, indicating that processing the data in a slice-wise fashion is a valuable simplification.

Table 1: MSE and AHD scores (formulas in Appendix D) for both directions of the mapping.

| Method | 3 T to 1.5 T | | 1.5 T to 3 T | |
	MSE	AHD	MSE	AHD
Original	1.85×10^{-3}	6.15×10^{5}	1.85×10^{-3}	6.15×10^{5}
DH	2.30×10^{-3}	7.49×10^{5}	1.73×10^{-3}	8.22×10^{5}
pGAN	$\mathbf{1.50 \times 10^{-3}}$	$\mathbf{1.27 \times 10^{5}}$	0.94×10^{-3}	2.07×10^{5}
DM (ours)	1.61×10^{-3}	1.31×10^{5}	$\mathbf{0.76 \times 10^{-3}}$	$\mathbf{1.48 \times 10^{5}}$

To compare the different methods, we compute the Mean Squared Error (MSE) between the ground truth images $\hat{B}$ and the translated images $B_{transformed}$. In Table 1 we report the MSE as well as the sum of the bin-wise absolute difference between the histograms (AHD). In Figure 5 we show exemplary histograms, each consisting of 255 bins, of B, $\hat{B}$ and the generated volumes $B_{transformed}$ for both directions of the image mapping. Translating images of 3 T to 1.5 T contrast, our DM and the $pGAN$ approach manage to decrease the MSE and to improve the AHD compared to *Original*. DH cannot compete and produces a higher MSE and AHD than the *Original*, also observable in the shift towards bright pixels in the histograms of Figure 5. Transforming 1.5 T to 3 T contrast, our DM outperforms

Figure 5: Exemplary histograms of $B \in \mathcal{S}$ and $\hat{B} \in \mathcal{T}$ and samples generated by DH, $pGAN$ and our DM for both directions of the translation. The histograms of the DH samples are cropped as they contain a comparatively high amount of white voxels.

Original, *DH* and *pGAN* regarding MSE and AHD. While *pGAN* still manages to considerably improve MSE and AHD compared to the *Original*, *DH* shows a bad performance with respect to those scores. This can also be seen in the visual comparison shown in Figures 4 and 5. The histogram of *DH* is shifted towards the brightest pixels and the histogram of our model aligns better with the histogram of ground truth $\hat{B}$ than *pGAN*.

Table 2: Absolute volume differences in mm³ of the segmentations of CSF, GM and WM of all original images $B \in \mathcal{S}$ and generated images $B_{transformed}$ compared to ground truths $\hat{B} \in \mathcal{T}$ for both directions of the mapping. The best result per class is bold.

Method	3 T to 1.5 T			1.5 T to 3 T		
	CSF	GM	WM	CSF	GM	WM
Original	3.72×10^4	9.32×10^4	8.88×10^4	3.72×10^4	9.32×10^4	8.88×10^4
pGAN	$\mathbf{1.12 \times 10^4}$	$\mathbf{1.14 \times 10^4}$	1.91×10^4	3.11×10^4	6.15×10^4	2.09×10^4
DM (ours)	1.95×10^4	1.54×10^4	$\mathbf{1.59 \times 10^4}$	$\mathbf{1.79 \times 10^4}$	$\mathbf{3.91 \times 10^4}$	$\mathbf{1.49 \times 10^4}$

To obtain further insight about the increased comparability of $B_{transformed}$ with $\hat{B} \in \mathcal{T}$, we segmented the original 3D images as well as the 3D images generated by our DM and $pGAN$ into the three classes CSF, GM and WM using FAST (Zhang et al., 2001). DH could not be considered for this comparison, as the quality of the generated images was not high enough to create meaningful segmentations using FAST. Examples of the segmentations can be found in Appendix F. We calculate the volume of each class by counting the voxels attributed to each class as the voxel size is $1 \times 1 \times 1$ mm³. For both directions of the image mapping we then compute the volume differences for each class between the ground truth segmentation of $\hat{B}$, and the segmentations of B or $B_{transformed}$, respectively. Table 2 shows that $pGAN$ and our DM decrease the differences between the segmentation volumes

of $B_{transformed}$ and $\hat{B}$ compared to the segmentation volume difference between B and $\hat{B}$ for both ways of the transformation. $pGAN$ and our DM show similar performance for the transformation from 3 T to 1.5 T but our model performs better for the transformation from 1.5 T to 3 T. The Dice scores of the FAST segmentations, summarized in Table 3, are high for the comparison of the segmentation of the original image B with the ground truth segmentation of $\hat{B}$. The Dice scores remain high for the comparison of the segmentations of $B_{transformed}$ generated by both, our DM and $pGAN$, with the ground truth segmentation of $\hat{B}$. This shows that the generated images do not only show a voxel intensity distribution and segmentation volumes very close to the ground truth, but are also consistent regarding the locations of the CSF, GM and WM.

Table 3: Dice score of segmentations of CSF, GM and WM of B and of $B_{transformed}$ compared to ground truth segmentation of $\hat{B}$ for both ways of translation.

	3 T to 1.5 T			1.5 T to 3 T		
Score	Original	pGAN	DM (ours)	Original	pGAN	DM (ours)
Dice	0.966	**0.966**	0.964	0.966	0.966	**0.972**

5. Conclusion

We present a novel method for contrast harmonization based on DDPMs. Using paired data from a source contrast $\mathcal{S}$ and a target contrast $\mathcal{T}$, our method allows us to translate a scan B of the source contrast $\mathcal{S}$ to scan $B_{transformed}$ appearing in the contrast of $\mathcal{T}$. For the image-to-image translation, our diffusion model receives information from the source image B, as we only want to adjust the contrast while keeping the anatomical information. The translation improves comparability between scans from different contrasts for further evaluation and downstream tasks such as tissue segmentation. Our model outperforms the comparing methods for the transformation from 1.5 T to 3 T and generates great results for the opposite translation. Compared to GANs, diffusion models are not trained in an adversarial manner, making the training straightforward. The input and output of our model are 2D slices, allowing us to save memory compared to models trained on 3D volumes. Stacking the 2D images to a 3D volume does not generate any stripe artifacts, showing us that our method only changes the contrast and not the anatomical structure. Due to the image generation characteristics of DDPMs, our method has a long sampling time compared to the other methods, which could be improved by using other sampling schemes (Song et al., 2020). So far, our model was only trained on skull-stripped data sets, limiting a more in-depth temporal analysis of brain-volume changes. As our next step, we will omit the skull-stripping during pre-processing, enabling observing brain-volume changes relative to the fixed skull size.

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References

Anonymous. Anonymous title. *Anonymous Journal*, 20xx.

Brian B Avants, Nicholas J Tustison, Michael Stauffer, Gang Song, Baohua Wu, and James C Gee. The insight toolkit image registration framework. *Frontiers in neuroinformatics*, 8:44, 2014.

Ahmed Ba-Ssalamah, Iris M Nöbauer-Huhmann, Katja Pinker, Nadja Schibany, Rupert Prokesch, Sheida Mehrain, Vladimir Mlynárik, Amura Fog, Karl Heimberger, and Siegfried Trattnig. Effect of contrast dose and field strength in the magnetic resonance detection of brain metastases. *Investigative radiology*, 38(7):415–422, 2003.

Mahsa Dadar, Simon Duchesne, CCNA Group, et al. Reliability assessment of tissue classification algorithms for multi-center and multi-scanner data. *NeuroImage*, 217:116928, 2020.

Salman UH Dar, Mahmut Yurt, Levent Karacan, Aykut Erdem, Erkut Erdem, and Tolga Cukur. Image synthesis in multi-contrast mri with conditional generative adversarial networks. *IEEE transactions on medical imaging*, 38(10):2375–2388, 2019.

Blake E Dewey, Can Zhao, Jacob C Reinhold, Aaron Carass, Kathryn C Fitzgerald, Elias S Sotirchos, Shiv Saidha, Jiwon Oh, Dzung L Pham, Peter A Calabresi, et al. Deepharmony: A deep learning approach to contrast harmonization across scanner changes. *Magnetic resonance imaging*, 64:160–170, 2019.

Prafulla Dhariwal and Alexander Nichol. Diffusion models beat gans on image synthesis. *Advances in Neural Information Processing Systems*, 34:8780–8794, 2021.

Zolnamar Dorjsembe, Sodtavilan Odonchimed, and Furen Xiao. Three-dimensional medical image synthesis with denoising diffusion probabilistic models. In *Medical Imaging with Deep Learning*. PMLR, 2022.

Hajar Emami, Majid Moradi Aliabadi, Ming Dong, and Ratna Babu Chinnam. Spa-gan: Spatial attention gan for image-to-image translation. *IEEE Transactions on Multimedia*, 23:391–401, 2020.

Ian Goodfellow, Jean Pouget-Abadie, Mehdi Mirza, Bing Xu, David Warde-Farley, Sherjil Ozair, Aaron Courville, and Yoshua Bengio. Generative adversarial nets. In Z. Ghahramani, M. Welling, C. Cortes, N. Lawrence, and K.Q. Weinberger, editors, *Advances in Neural Information Processing Systems*, volume 27. Curran Associates, Inc., 2014.

Jonathan Ho, Ajay Jain, and Pieter Abbeel. Denoising diffusion probabilistic models. *Advances in Neural Information Processing Systems*, 33:6840–6851, 2020.

Fabian Isensee, Marianne Schell, Irada Pflueger, Gianluca Brugnara, David Bonekamp, Ulf Neuberger, Antje Wick, Heinz-Peter Schlemmer, Sabine Heiland, Wolfgang Wick, et al. Automated brain extraction of multisequence mri using artificial neural networks. *Human brain mapping*, 40(17):4952–4964, 2019.

Phillip Isola, Jun-Yan Zhu, Tinghui Zhou, and Alexei A Efros. Image-to-image translation with conditional adversarial networks. In *Proceedings of the IEEE conference on computer vision and pattern recognition*, pages 1125–1134, 2017.

Tero Karras, Miika Aittala, Samuli Laine, Erik Härkönen, Janne Hellsten, Jaakko Lehtinen, and Timo Aila. Alias-free generative adversarial networks. *Advances in Neural Information Processing Systems*, 34:852–863, 2021.

Shiva Keihaninejad, Rolf A Heckemann, Gianlorenzo Fagiolo, Mark R Symms, Joseph V Hajnal, Alexander Hammers, Alzheimer's Disease Neuroimaging Initiative, et al. A robust method to estimate the intracranial volume across mri field strengths (1.5 t and 3t). *Neuroimage*, 50(4):1427–1437, 2010.

Boah Kim, Inhwa Han, and Jong Chul Ye. Diffusemorph: Unsupervised deformable image registration using diffusion model. In *European Conference on Computer Vision*, pages 347–364. Springer, 2022.

Julia Krüger, Roland Opfer, Nils Gessert, Ann-Christin Ostwaldt, Praveena Manogaran, Hagen H Kitzler, Alexander Schlaefer, and Sven Schippling. Fully automated longitudinal segmentation of new or enlarged multiple sclerosis lesions using 3d convolutional neural networks. *NeuroImage: Clinical*, 28:102445, 2020.

Hyunwoo Lee, Kunio Nakamura, Sridar Narayanan, Robert A Brown, Douglas L Arnold, Alzheimer's Disease Neuroimaging Initiative, et al. Estimating and accounting for the effect of mri scanner changes on longitudinal whole-brain volume change measurements. *Neuroimage*, 184:555–565, 2019.

Xiaoming Liu, Aihui Yu, Xiangkai Wei, Zhifang Pan, and Jinshan Tang. Multimodal mr image synthesis using gradient prior and adversarial learning. *IEEE Journal of Selected Topics in Signal Processing*, 14(6):1176–1188, 2020.

Andreas Lugmayr, Martin Danelljan, Andres Romero, Fisher Yu, Radu Timofte, and Luc Van Gool. Repaint: Inpainting using denoising diffusion probabilistic models. In *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition*, pages 11461–11471, 2022.

Yanmei Luo, Dong Nie, Bo Zhan, Zhiang Li, Xi Wu, Jiliu Zhou, Yan Wang, and Dinggang Shen. Edge-preserving mri image synthesis via adversarial network with iterative multi-scale fusion. *Neurocomputing*, 452:63–77, 2021.

Qing Lyu and Ge Wang. Conversion between ct and mri images using diffusion and score-matching models. *arXiv preprint arXiv:2209.12104*, 2022.

Don H Mahad, Bruce D Trapp, and Hans Lassmann. Pathological mechanisms in progressive multiple sclerosis. *The Lancet Neurology*, 14(2):183–193, 2015.

Antoine J Maubon, Jean-Michel Ferru, Vincent Berger, Marie Colette Soulage, Marc De-Graef, Pierre Aubas, Patrice Coupeau, Erik Dumont, and Jean-Pierre Rouanet. Effect of field strength on mr images: comparison of the same subject at 0.5, 1.0, and 1.5 t. *Radiographics*, 19(4):1057–1067, 1999.

Alexander Quinn Nichol and Prafulla Dhariwal. Improved denoising diffusion probabilistic models. In *International Conference on Machine Learning*, pages 8162–8171. PMLR, 2021.

Dong Nie, Roger Trullo, Jun Lian, Caroline Petitjean, Su Ruan, Qian Wang, and Dinggang Shen. Medical image synthesis with context-aware generative adversarial networks. In *International conference on medical image computing and computer-assisted intervention*, pages 417–425. Springer, 2017.

Dong Nie, Roger Trullo, Jun Lian, Li Wang, Caroline Petitjean, Su Ruan, Qian Wang, and Dinggang Shen. Medical image synthesis with deep convolutional adversarial networks. *IEEE Transactions on Biomedical Engineering*, 65(12):2720–2730, 2018.

Muzaffer Özbey, Salman UH Dar, Hasan A Bedel, Onat Dalmaz, Şaban Özturk, Alper Güngör, and Tolga Çukur. Unsupervised medical image translation with adversarial diffusion models. *arXiv preprint arXiv:2207.08208*, 2022.

Bo Peng, Bingzheng Liu, Yi Bin, Lili Shen, and Jianjun Lei. Multi-modality mr image synthesis via confidence-guided aggregation and cross-modality refinement. *IEEE Journal of Biomedical and Health Informatics*, 26(1):27–35, 2021.

Walter HL Pinaya, Petru-Daniel Tudosiu, Jessica Dafflon, Pedro F Da Costa, Virginia Fernandez, Parashkev Nachev, Sebastien Ourselin, and M Jorge Cardoso. Brain imaging generation with latent diffusion models. In *MICCAI Workshop on Deep Generative Models*, pages 117–126. Springer, 2022.

Robin Rombach, Andreas Blattmann, Dominik Lorenz, Patrick Esser, and Björn Ommer. High-resolution image synthesis with latent diffusion models. In *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition*, pages 10684–10695, 2022.

Olaf Ronneberger, Philipp Fischer, and Thomas Brox. U-net: Convolutional networks for biomedical image segmentation. In *International Conference on Medical image computing and computer-assisted intervention*, pages 234–241. Springer, 2015.

Chitwan Saharia, William Chan, Huiwen Chang, Chris Lee, Jonathan Ho, Tim Salimans, David Fleet, and Mohammad Norouzi. Palette: Image-to-image diffusion models. In *ACM SIGGRAPH 2022 Conference Proceedings*, pages 1–10, 2022a.

Chitwan Saharia, William Chan, Saurabh Saxena, Lala Li, Jay Whang, Emily Denton, Seyed Kamyar Seyed Ghasemipour, Burcu Karagol Ayan, S Sara Mahdavi, Rapha Gontijo Lopes, et al. Photorealistic text-to-image diffusion models with deep language understanding. *arXiv preprint arXiv:2205.11487*, 2022b.

Junyoung Seo, Gyuseong Lee, Seokju Cho, Jiyoung Lee, and Seungryong Kim. Midms: Matching interleaved diffusion models for exemplar-based image translation. *arXiv preprint arXiv:2209.11047*, 2022.

Tim Sinnecker, Sabine Schädelin, Pascal Benkert, Esther Ruberte, Michael Amann, Johanna M Lieb, Yvonne Naegelin, Jannis Müller, Jens Kuhle, Tobias Derfuss, et al. Brain atrophy measurement over a mri scanner change in multiple sclerosis. *NeuroImage: Clinical*, 36:103148, 2022.

Stephen M Smith, Yongyue Zhang, Mark Jenkinson, Jacqueline Chen, Paul M Matthews, Antonio Federico, and Nicola De Stefano. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage*, 17(1):479–489, 2002.

Stephen M Smith, Mark Jenkinson, Mark W Woolrich, Christian F Beckmann, Timothy EJ Behrens, Heidi Johansen-Berg, and PM Matthews. Advances in functional and structural mr image analysis and implementation as fsl technical report tr04ss2. *Neuroimage*, 23 (S1):208–219, 2004.

Jascha Sohl-Dickstein, Eric Weiss, Niru Maheswaranathan, and Surya Ganguli. Deep unsupervised learning using nonequilibrium thermodynamics. In *International Conference on Machine Learning*, pages 2256–2265. PMLR, 2015.

Jiaming Song, Chenlin Meng, and Stefano Ermon. Denoising diffusion implicit models. *arXiv preprint arXiv:2010.02502*, 2020.

Nicholas J Tustison, Brian B Avants, Philip A Cook, Yuanjie Zheng, Alexander Egan, Paul A Yushkevich, and James C Gee. N4itk: improved n3 bias correction. *IEEE transactions on medical imaging*, 29(6):1310–1320, 2010.

Julia Wolleb, Florentin Bieder, Robin Sandkühler, and Philippe C. Cattin. Diffusion models for medical anomaly detection. In *International Conference on Medical image computing and computer-assisted intervention*, page 35–45. Springer, 2022a.

Julia Wolleb, Robin Sandkuehler, Florentin Bieder, Philippe Valmaggia, and Philippe C. Cattin. Diffusion models for implicit image segmentation ensembles. In *Medical Imaging with Deep Learning*, pages 1336–1348. PMLR, 2022b.

Julia Wolleb, Robin Sandkühler, Florentin Bieder, and Philippe C Cattin. The swiss army knife for image-to-image translation: Multi-task diffusion models. *arXiv preprint arXiv:2204.02641*, 2022c.

Yongyue Zhang, Michael Brady, and Stephen Smith. Segmentation of brain mr images through a hidden markov random field model and the expectation-maximization algorithm. *IEEE transactions on medical imaging*, 20(1):45–57, 2001.

Jun-Yan Zhu, Taesung Park, Phillip Isola, and Alexei A Efros. Unpaired image-to-image translation using cycle-consistent adversarial networks. In *Proceedings of the IEEE international conference on computer vision*, pages 2223–2232, 2017.

Appendix A. Scanner Details

Table 4: MR Scanners used for the data acquisition (Anonymous, 20xx)

	Previous Scanner	**Current Scanner**
Manufacturer	Siemens Healthineers	Siemens Healthineers
	Erlangen, Germany	Erlangen, Germany
Model Name	Magnetom Avanto	Magnetom Skyra^{fit}
Magnetic Field Strength	1.5 T	3 T
Repetition Time	2080 ms	2300 ms
Inversion Time	1100 ms	900 ms
Echo Time	3.1 ms	2.94 ms
Sequence used for Data Set	MPRAGE	MPRAGE
SMSC Scan Period	2012 - 2016	2016 - present

Appendix B. Data Set Details

The MS patients are part of a longitudinal MS study (Anonymous, 20xx). Both, MS patients and healthy controls were scanned first in the 1.5 T scanner and after the scanner change in the 3 T scanner (median time interval 3.5 months, range 1.7 – 5.2 months).

Table 5: Details about the participants included in the data set, provided by (Anonymous, 20xx)

	Multiple Sclerosis	**Healthy Controls**
Number of Female Participants	14	11
Number of Male Participants	4	11
Age in Years, Mean [SD]	51.7 [$\pm$12.7]	28.9 [$\pm$7.6]

Appendix C. Implementation Details

We compared our models against DeepHarmony and pGAN. For both comparing methods, we used the same four train and test folds as for our model to perform cross-validation. Implementation details:

- DeepHarmony: To make it more comparable to our method, we used 2D sagittal slices with shape [256, 256] as input, instead of the 2.5 dimensional implementation proposed in the paper. We cropped the output to [224, 224] and stacked the slices to a 3D volume of shape [160, 224, 224]. We trained the model for 300 epochs. We used a batch size of eight as in the original implementation and adjusted the learning rate to 10^{-4} as the original learning rate was not compatible with our images. For further implementation details refer to (Dewey et al., 2019).

- pGAN: we trained the models for 300 epochs (150 with normal learning rate, 150 with the learning rate decayed to zero) with a batch size of four. We used no neighbouring slices. The cycle loss weight as well as the perceptual loss weight were set to 100. The processed slices were of shape [256, 256], we cropped and stacked the output slices to shape [160, 224, 224] for comparison with our model. For further implementation details refer to (Dar et al., 2019) and https://github.com/icon-lab/pGAN-cGAN.

Appendix D. Detailed Metrics

The MSE was calculated using

$$MSE = \sum_{i=1}^{N}(a_i - b_i)^2 \tag{6}$$

with a and b being the images to compare and i iterating over all pixels N. The squared differences are summed. To calculate the AHD we used the following formula

$$AHD = \sum_{i=1}^{bins} \mid h_1(x_i) - h_2(x_i) \mid \tag{7}$$

with h_1 and h_2 being the histograms to compare for all bins x_i, with i ranging from one to the total number of bins.

Table 6: MSE and AHD averages including variances over four-fold cross-validation for the translation from 3 T to 1.5 T contrast.

Method	MSE	AHD
Original	$1.85[\pm0.03] \times 10^{-3}$	$6.15[\pm0.12] \times 10^5$
DH	$2.30[\pm0.07] \times 10^{-3}$	$7.49[\pm0.09] \times 10^5$
pGAN	$\mathbf{1.50[\pm0.03] \times 10^{-3}}$	$\mathbf{1.27[\pm0.07] \times 10^5}$
DM (ours)	$1.61[\pm0.03] \times 10^{-3}$	$1.31[\pm0.16] \times 10^5$

Table 7: MSE and AHD averages including variances over four-fold cross-validation for the translation from 1.5 T to 3 T contrast.

Method	MSE	AHD
Original	$1.85[\pm0.03] \times 10^{-3}$	$6.15[\pm0.12] \times 10^5$
DH	$1.73[\pm0.07] \times 10^{-3}$	$8.22[\pm0.14] \times 10^5$
pGAN	$0.94[\pm0.11] \times 10^{-3}$	$2.07[\pm0.34] \times 10^5$
DM (ours)	$\mathbf{0.76[\pm0.008] \times 10^{-3}}$	$\mathbf{1.48[\pm0.16] \times 10^5}$

Table 8: Average segmentation differences and variances of the four-fold cross-validation. Differences between $\hat{B}$ and B as well as between $\hat{B}$ and $B_{transformed}$, for the translation from 3 T to 1.5 T contrast.

Method	CSF	GM	WM
Original	$3.72[\pm 0.43] \times 10^4$	$9.32[\pm 0.93] \times 10^4$	$8.88[\pm 0.58] \times 10^4$
pGAN	$\mathbf{1.12[\pm 0.17] \times 10^4}$	$\mathbf{1.41[\pm 0.23] \times 10^4}$	$1.91[\pm 0.19] \times 10^4$
DM (ours)	$1.95[\pm 0.24] \times 10^4$	$1.54[\pm 0.40] \times 10^4$	$\mathbf{1.59[\pm 0.24] \times 10^4}$

Table 9: Average segmentation differences and variances of the four-fold cross-validation. Differences between $\hat{B}$ and B as well as between $\hat{B}$ and $B_{transformed}$, for the translation from 1.5 T to 3 T contrast.

Method	CSF	GM	WM
Original	$3.72[\pm 0.43] \times 10^4$	$9.32[\pm 0.93] \times 10^4$	$8.88[\pm 0.58] \times 10^4$
pGAN	$3.11[\pm 0.55] \times 10^4$	$6.15[\pm 0.51] \times 10^4$	$2.10[\pm 0.27] \times 10^4$
DM (ours)	$\mathbf{1.79[\pm 0.06] \times 10^4}$	$\mathbf{3.91[\pm 0.19] \times 10^4}$	$\mathbf{1.49[\pm 0.65] \times 10^4}$

Table 10: Average Dice scores and variances of segmentations of CSF, GM and WM of B and of $B_{transformed}$ compared to ground truth segmentation of $\hat{B}$ for the translation form 3 T to 1.5 T.

Score	Original	pGAN	DM (ours)
Dice	$0.966[\pm 0.0013]$	$\mathbf{0.966[\pm 0.0009]}$	$0.964[\pm 0.0008]$

Table 11: Average Dice scores and variances of segmentations of CSF, GM and WM of B and of $B_{transformed}$ compared to ground truth segmentation of $\hat{B}$ for the translation form 1.5 T to 3 T.

Score	Original	pGAN	DM (ours)
Dice	$0.966[\pm 0.0013]$	$0.966[\pm 0.0006]$	$\mathbf{0.972[\pm 0.0009]}$

Appendix E. Image Examples

3 T Original B
(Input)

1.5 T Original
$\hat{B}$ (GT)

$B_{transformed}$ by
DH

$B_{transformed}$ by
pGAN

$B_{transformed}$ by
our DM

Figure 6: Exemplary images for the translation from 3 T source contrast to 1.5 T target contrast.

*1.5 T Original
B (Input)*

*3 T Original
$\hat{B}$ (GT)*

$B_{transformed}$ *by
DH*

$B_{transformed}$ *by
pGAN*

$B_{transformed}$ *by
our DM*

Figure 7: Exemplary images for the translation from 1.5 T source contrast to 3 T target contrast.

Appendix F. Segmentation Examples

Segmentation of
3 T Original B (Input)

Segmentation of
1.5 T Original $\hat{B}$ (GT)

Segmentation of
$B_{transformed}$ by pGAN

Segmentation of
$B_{transformed}$ by our DM

Figure 8: Exemplary segmentations for the translation from 3 T source contrast to 1.5 T target contrast.

*Segmentation of
1.5 T Original B (Input)*

*Segmentation of
3 T Original $\hat{B}$ (GT)*

*Segmentation of
$B_{transformed}$ by pGAN*

*Segmentation of
$B_{transformed}$ by our DM*

Figure 9: Exemplary segmentations for the translation from 1.5 T source contrast to 3 T target contrast.