Simulation-based evaluation framework for deep learning unsupervised anomaly detection on brain FDG PET

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ABSTRACT

Unsupervised anomaly detection using deep learning models is a popular computer-aided diagnosis approach because it does not need annotated data and is not restricted to the diagnosis of a disease seen during training. Such approach consists in first learning the distribution of anomaly free images. Images presenting anomalies are then detected as outliers of this distribution. These approaches have been widely applied in neuroimaging to detect sharp and localized anomalies such as tumors or white matter hyper-intensities from structural MRI. In this work, we aim to detect anomalies from FDG PET images of patients with Alzheimer's disease. In this context, the anomalies can be subtle and difficult to delineate, making the task more difficult and meaning that no ground truth exists to evaluate the approaches. We thus propose a framework to evaluate unsupervised anomaly detection approaches that consists in simulating realistic anomalies from images of healthy subjects. We demonstrate the use of this framework by evaluating an approach based on a 3D variational autoencoder.

Keywords: Unsupervised anomaly detection, Deep generative models, PET, Alzheimer's disease, Simulation framework

1. INTRODUCTION

As the global population gets older, we might face more cases of Alzheimer's disease (AD) and other types of dementia,[1] with an increase in social and financial costs.[2] Neurodegeneration caused by these diseases is visible on several imaging modalities,[3] including ^{18}F-fluorodeoxyglucose (FDG) PET in the form of hypo-metabolism.[4] By displaying subtle changes in brain metabolism, FDG PET can help the early diagnosis of dementia.

Recent breakthroughs in deep learning have offered many new possibilities in medical image analysis and algorithms are now able to accomplish complex tasks[5] such computer-aided diagnosis. A now widely used approach is unsupervised anomaly detection (UAD). The underlying idea is to learn the distribution of normal data and then try to detect out-of-distribution samples,[6] and thus identify abnormal cases. The first advantage of this method is that is does not require voxel-level annotation; another benefit is that the model should be able to detect any type of anomalies, without having seen them before.

One way of applying UAD to medical images is to train generative models such as variational autoencoders (VAE)[7] or generative adversarial networks[8] to synthesize healthy looking images. Such model is only trained with images from subjects diagnosed as healthy. The assumption made is that if the model only learns to reconstruct healthy images, then the reconstruction of abnormal images will be inaccurate (and will ideally look healthy). The comparison of real and generated images should enable the detection and localization of pathological areas. We can distinguish two different objectives: the first one is to reconstruct an image that corresponds to the subject under investigation, and the second one is to generate images that look healthy.[9]

UAD has been widely applied to neuroimaging data to detect anomalies that are sharp and localized such as tumors or white matter hyper-intensities on structural MRI.[10] However, applying UAD to dementia is more challenging because the lesions, e.g., metabolic changes on FDG PET, are more diffuse and less intense. Moreover,

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there are no masks for anomalies to use as ground truth to evaluate UAD models. Therefore most of the studies rely on residual error,[11] which does not allow a precise evaluation of the model's capabilities.

We propose a new framework for the evaluation of UAD applied to dementia using synthetic data: we simulate anomalies on healthy images to generate a test set with both the diseased image and its healthy version. We then apply this framework to evaluate a new 3D VAE for UAD on FDG PET scans for dementia.

2. METHOD AND MATERIALS

2.1 Dataset

FDG PET scans used in this study were obtained from the ADNI database.[12,13] We selected images co-registered, averaged and uniformized to the same resolution to reduce the variability due to the use of different cameras. PET images were then processed using Clinica:[14] they were linearly registered to the standard MNI space, normalized in intensity using the average PET uptake in a region comprising cerebellum and pons, and cropped.

In ADNI, there is a total of 3511 FDG PET scans from 1600 participants. Since UAD models are trained only on healthy images, we selected the 301 cognitively normal (CN) subjects (733 images). We also selected the 311 baseline sessions of AD patients for testing purposes. All the other participants were discarded.

2.2 Simulation-based evaluation framework

To evaluate the quality of the reconstruction, four metrics are often used in the literature:[15] the mean absolute error (MAE), the mean squared error (MSE), the peak signal-to-noise ratio (PSNR) and the structural similarity index (SSIM).[16] But if these metrics can be used to measure the conservation of the subject identity, they are not suited to evaluate healthiness of the synthesized images.

To tackle this issue, we generated a new test set by simulating hypo-metabolism on healthy images to have pairs of healthy (considered as ground truth) and diseased images. For this purpose, we designed a mask corresponding to regions associated with AD (parietal and temporal lobes)[17] that were extracted from the AAL3 atlas.[18] To obtain a realistic synthetic image, we smoothed the mask with a Gaussian convolution filter of $\sigma = 5$. We then reduced the intensity of the PET scan within the region defined by the mask by different factors to simulate various degrees of hypo-metabolism. Having such pairs of images allows comparing images reconstructed by the model from images presenting anomalies with their corresponding healthy images, hence better evaluating the model capacity to synthesize pseudo-healthy scans.

To ensure that the UAD model being evaluated can generalize to dementias other than AD, we generated masks corresponding to five other dementias: behavioral variant frontotemporal dementia (bvFTD), logopenic variant primary progressive aphasia (lvPPA), semantic variant PPA (svPPA), nonfluent variant PPA (nfvPPA) and posterior cortical atrophy (PCA) based on the regions defined by Burgos et al.[19]

2.3 3D variational autoencoder

To synthesize pseudo-healthy images, we proposed a 3D variational autoencoder that we trained on images from CN subjects to learn their distribution. A VAE is a deep probabilistic model[7] that aims to approximate the true distribution of the data with a simple parameterized distribution. To this end, all the samples $\mathbf{x}$ from the dataset will be projected through an encoder in a latent space of smaller dimension in which each sample $\mathbf{x}$ will be mapped to a Gaussian distribution $\mathcal{N}(\mu(\mathbf{x}), \sigma(\mathbf{x}))$. Then, the decoder will learn to reconstruct the input data from the latent representation z that will be sampled from this distribution. Let's note $\hat{\mathbf{x}}$ the reconstruction of $\mathbf{x}$, our loss function will be the sum of the L_2 loss and the Kullback-Leiber divergence between our distribution and the normal distribution $\mathcal{N}(0, 1)$, which can be simplified in Equation 1 as

$$\mathcal{L}(\mathbf{x}, \hat{\mathbf{x}}) = L_2(\mathbf{x}, \hat{\mathbf{x}}) - \frac{1}{2}\left[\sigma(\mathbf{x})^2 + \mu(\mathbf{x})^2 - \log(\sigma(\mathbf{x})^2) - 1\right] \quad . \tag{1}$$

2.4 Experimental settings

We split our dataset of 301 CN subjects into training, validation and test sets at the subject's level to avoid any form of data leakage.[20] The split is stratified by sex and age to reduce biases. 30 CN subjects compose the test set that is used to assess whether the healthy images are reconstructed as healthy. Then in each fold of the 8-fold cross validation, 34 subjects belong to the validation set to monitor the training and 237 subjects are used to train our models. This represents between 563 and 592 images for the training phase depending on the fold. In addition to CN subjects, we use the images of 311 AD patients acquired at baseline to create a second test set. The model was trained on the eight folds, but as the results were very similar on all the folds, we will only report the results on the first fold.

The encoder of the 3D VAE we implemented is composed of three convolutional layers and one dense layer, and the decoder is symmetrical. We used batch normalization after each convolutional layer and a leaky-ReLU activation function after each normalization. We empirically chose a latent space of size 128. The model was trained on 300 epochs, with a learning rate of 10^{-5} using the ClinicaDL[21] software. Note that the images were down-sampled to a $80 \times 96 \times 80$ voxel size in order to reduce their dimension and the memory needed, which allowed increasing the batch size to 24.

3. RESULTS

3.1 Results on simulated AD-like FDG PET images

To evaluate the impact of the anomaly severity, we simulated different degrees of hypo-metabolism from 5% to 70% (Figure 1). We see that the MSE between the input and the output images is higher for more severe anomalies. This is expected as it means that the model cannot reconstruct well highly abnormal areas, and so should be able to detect them. We compared the MSE obtained on simulated data to that obtained when feeding images from the CN test set as inputs, which contain no anomaly. We observe that for low degree hypo-metabolism (<20%), the MSE are similar to that obtained for the CN test set. This means that the residual error due to the model imperfect reconstruction dissimulates the reconstruction error due to low degree anomalies.[22]

To confirm our observations, we computed a t-test assessing whether there was a significant difference in MSE between using healthy images as inputs and using images with various degrees of anomalies. The p-values were corrected for multiple comparisons using the Bonferroni method (the difference is statistically significant when p-value $< 0.05/9 = 0.0056$). The difference in MSE becomes significant for anomalies of degree 25 % and above. This corroborates the results of Landau et al[17] who defined that, on average in the ADNI dataset, the difference in metabolism between CN subjects and AD patients is ∼25% in a region of interest relevant to AD.

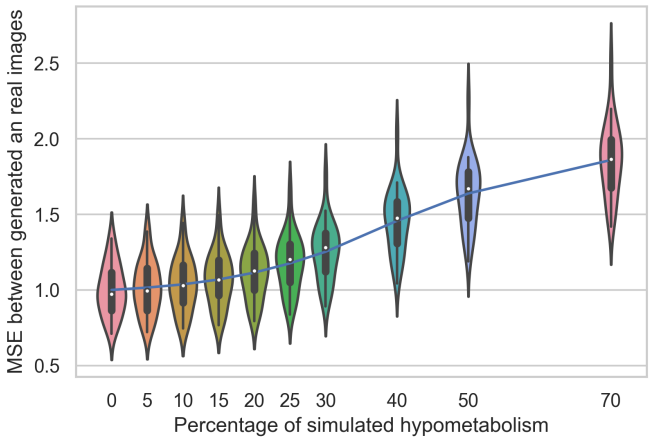

Figure 1: Evolution of the MSE with increasing degrees of hypo-metabolism simulating AD-like anomalies. Each MSE is normalized by the average MSE obtained when reconstructing from the original healthy images.

	MSE	MAE	PSNR	SSIM
AD	0.00356	0.0414	24.6	0.729
bvFTD	0.00313	0.0388	25.2	0.741
lvPPA	0.00320	0.0392	25.1	0.739
svPPA	0.00293	0.0375	25.5	0.749
nfvPPA	0.00319	0.0388	25.2	0.744
PCA	0.00306	0.0381	25.4	0.749

Table 1: Reconstruction metrics computed between the original healthy PET scans from CN subjects in the test set and the images reconstructed with the 3D VAE from the hypo-metabolic scans simulating different types of dementia.

In Figure 2, we plotted the real image of a CN subject and its pseudo-healthy reconstruction, and the simulated AD version (with a hypo-metabolism degree of 30%) and its reconstruction for the same CN subject, together with the residual images. We observe that the input and output images of the CN subject are quite similar. The differences are due to the model imperfect reconstruction and correspond to the minimal error that it can achieve. When feeding the simulated hypo-metabolic image to the model, we observe that the reconstructed image looks healthier than the input image. The areas highlighted in the residual map correspond to the regions where hypo-metabolism was simulated. An interesting point also is that both images reconstructed from the same CN subject (either from the original image or the simulated hypo-metabolic one) are almost identical with a SSIM of 0.993. This shows that the model reconstructs the same image for the same subject whether the input image is healthy or presents anomalies.

3.2 Results when simulating various types of dementia

In this section, the degree of hypo-metabolism is set to 30% but the brain region where it is simulated changes to reflect various types of dementia. We report in Table 1 the different reconstruction metrics computed between the original PET scans from CN subjects in the test set and the images reconstructed from the hypo-metabolic scans simulating the different types of dementia. We observe that the metrics are similar for all the simulated dementias. We also computed the metrics between the images reconstructed from the original healthy scans and the images reconstructed from the simulated hypo-metabolic scans. Both reconstructions are almost identical with an SSIM on average superior to 0.99. We can conclude from this experiment that the model is able to reconstruct the healthy version of an image independently of the nature of the dementia that causes the anomaly.

3.3 Results on real images from the ADNI dataset

As final experiment, we compared the reconstructions obtained from the CN subjects from the test set and the AD patients. We can see in Table 2 that the reconstruction is on average better for CN subjects than AD patients, which is what we expect. In Figure 2, we also plotted the real image and the pseudo-healthy reconstruction for an AD patient and a CN subject from ADNI. We can observe that reconstruction quality is satisfactory for a very simple 3D model as we can recognize the subject in the output image. If we look at the AD patient, it seems like the model corrects the hypo-metabolism that we can observe in the PET scan, which is particularly visible on the bottom left corner of the axial slice and the left part of the coronal slice.

	MSE	MAE	PSNR	SSIM
AD test	0.00408	0.0433	24.5	0.709
CN test	0.00292	0.0373	25.6	0.749

Table 2: Reconstruction metrics obtained for real images of CN subjects and AD patients from ADNI (on the test set only).

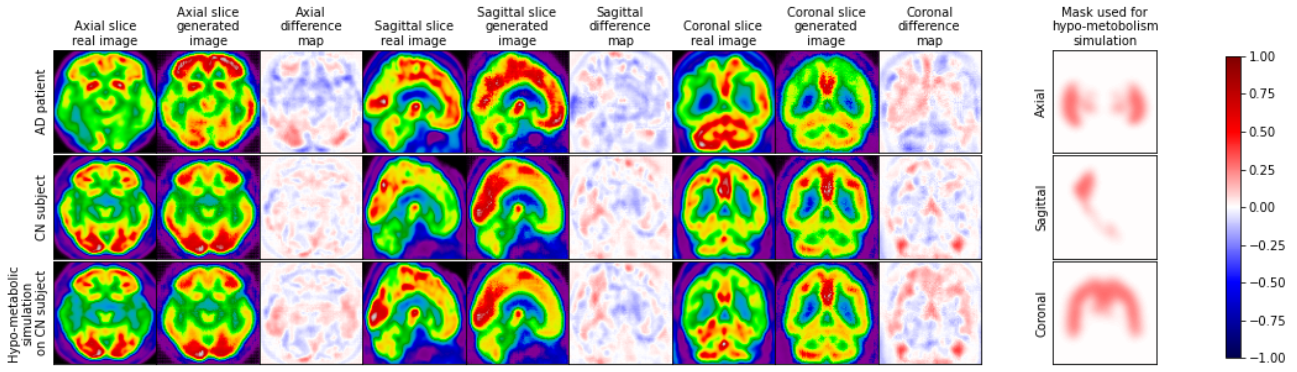

Figure 2: Example of results obtained from a real image of an AD patient (top row), a real image of a CN subject (middle row) and an image simulating AD hypo-metabolism based on the same CN subject (bottom row). For each plane, the first image is the input, the second one the model's reconstruction and the third one the difference (reconstruction - input).

4. DISCUSSION & CONCLUSION

The framework we proposed for UAD evaluation consists in simulating different types of dementia from a healthy PET image by reducing the intensity within a mask corresponding to regions known to be affected by the disease.

This allows us to obtain pairs of healthy ground truth and abnormal images to evaluate UAD models.

We simulated with this method different degrees of anomalies and different types of dementia to evaluate an UAD approach in different conditions. We could for example show that the model tested can detect anomalies of similar severity as found in a real AD dataset. We could also see that the images reconstructed from a healthy image or its simulated hypo-metabolic version are almost identical, which means that the model reconstructs a healthy version of the diseased image. We could improve this approach by adding more variability in the simulated diseased images by choosing sub-regions or randomly sampling the severity of the anomaly.

Finally, we showed that the simple 3D VAE we proposed leads to acceptable results in terms of reconstruction even though the results could be improved. We could enhance the VAE reconstruction capability by choosing a better posterior distribution approximation, adding a discriminator to the VAE to sharpen its output, or trying other autoencoder based models such as the adversarial autoencoder.

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The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD.

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