Diagnosing and Predicting the Progression of Alzheimer's Disease through Computerized Image Analysis of Magnetic Resonance Images

Muhammad Febrian Rachmadi
febrian.rachmadi@gmail.com, s1467961@sms.ed.ac.uk
The University of Edinburgh

Alzheimer's disease (AD) is the most common form of dementia that causes several symptoms including memory loss and difficulties in other cognitive areas [1]. Clinically, AD is hard to be detected and sometimes overlooked because symptoms are mild at earlier stages of the disease. Hence, most patients are diagnosed with AD in advanced stages of the disease. Some of the earlier symptoms of AD are memory lapses, loss in familiar places and difficulty in finding words which make daily life disrupted [2]. The progression of AD itself is different for each patient, and it depends on the impact of brain damage, patient's personality and state of health [3]. The 2010 World Alzheimer's report estimated 35.6 million people living with dementia. To accelerate research on AD, an initiative collaborative effort named Alzheimer's Disease Neuroimaging Initiative (ADNI) [4] started since October 2004. ADNI has propitiated a large amount of cross-validation between studies and the discovery of new biomarkers for clinical trials and diagnosis of AD. One of the biomarkers, which is a biological signature that can be used as an indicator of a pathological situation, is magnetic resonance imaging (MRI).

Diagnosing AD and predicting its progression have been challenges until now. The reason is simple: we cannot predict how a damaged region in the brain (i.e. "lesion") will expand and affect the cognitive skills of the individual. We have already known that the brain has millions, if not billions, inter-connected neurons that make a huge network that controls our body. We have also known that certain regions in the brain "control" particular body parts so that each region has its own purpose. However, lesions characteristics of AD might appear in any region of the brain. This interesting characteristic makes understanding AD more challenging than some other diseases in which brain lesions are also a trait, such as tumor and traumatic brain injury, because instead of only one lesion there are quite a diverse spectrum of them with likelihood of occurrence almost everywhere.

Since the discovery and widespread use of MRI, computer vision and image analysis have been used as major tools to understand abnormalities inside the brain. MRI scans provide better visualisation on what is happening inside the human brain, making easier for physicians to diagnose AD. The most common type of brain "lesion" in AD is known as white matter hyper intensities (WMH) in MRI. WMH appear as white voxels in two types of MR images namely T2-weighted and Fluid Attenuation Inversion Recovery (FLAIR). It is believed that WMH indicate ischemic injury and progression to dementia [5]. However, their presence in the context of AD is still unclear in terms of their relative contribution for explaining the mechanism of cognitive loss [6]. WMH are also commonly observed in aging individuals, where slight cognitive problems can be considered normal up to some extent [7]. It is hoped that better quantification of WMH in MRI may result on better understanding of their impact and dynamic, so that mechanisms to prolong brain health can be discovered.

WMH not only appear in MR image of AD patients and normal ageing individuals but also in images from other brain diseases, for example multiple sclerosis (MS). The difference between WMH in AD and MS is while the nature of hyperintensities in AD is still not clear, hyperintensities in MS usually represent inflammatory lesions indicative of the disease's phase [8]. Furthermore, it is expected to be more challenging if the patient has clinical symptoms of different brain diseases at the same time. In general, the similarity of the appearance of this biomarker in MRI across different diseases makes challenging to differentiate the ones that could be associated with each disease at the same time.

The ideas of quantifying damaged regions of WMH automatically and standardising the quantification of WMH have been identified as key to study disease progression of brain disease. Several methods and schemes have been proposed independently to do automatic segmentation of WMH for different diseases such as TBI [9], MS [10] and AD [11] using computer vision techniques. For many years, the biggest questions in automatic WMH segmentation works are 'What are the best features that represent WMH?' and 'What is the best method to do WMH segmentation given features and a set of data?' To answer the first question, feature extraction methods in computer vision that have been developed for natural images were used and tested extensively in previous works of WMH segmentation in MRI. Features such as greyscale values [11], histogram information [12] and texture based features [11][13] were tested to figure out the best possible set of features to use for WMH segmentation. On the other hand, different machine learning methods such as k-nearest neighbor (k-NN) [10], support vector machine (SVM) [11][12] and random forest (RF) [11] have also been tested using different feature extraction methods as the ones just mentioned. Previous studies reported that a set of combined features with RF machine learning method performed best for WMH segmentation. It is believed that RF performed better than the others because it can capture the importance of discriminative features in classification problem.

While it is possible to find the best combination of features from classical computer vision and machine learning method to do WMH segmentation, it is not an easy task as there are many possibilities of doing it. For my MSc degree, I evaluated the performance of three schemes that have reported best results for WMH segmentation on scans of AD patients so far, which have been done by Ithapu *et al.* [11], Leite *et al.* [12] and Klöppel *et al.* [13]. The results I obtained show that there is an essential limitation to these approaches especially in segmenting WMH in their early stages where the best scheme yielded high rates of precision and recall yet it yielded low Dice similarity coefficients. Overall, the results obtained mean that these approaches struggle to find correct segmentation of the WMH while making sure that non-WMH regions are correctly segmented as non-WMH. I believe that this weakness is caused by very subtle changes of values between the features that differentiate WMH and non-WMH regions. Based on my previous work, I strongly believe that classical feature extractions in computer vision are not enough to represent WMH.

To tackle this problem, a more sophisticated method in computer vision named deep learning might be the best choice for future studies in medical image analysis. The idea of deep learning is to find the best possible feature from a given dataset and use the resulted feature for classification, or segmentation in our case. Deep learning approaches have been studied, tested and used extensively in computer vision fields especially in natural image problems, such as segmentation and colourisation. However, it is not the case in analysis of MRI where the number of studies using this method is still limited. Two examples of studies

that applied deep learning in medical image analysis are brain tumor segmentation with deep neural networks [14] and classification of AD/non-AD MRI using deep Boltzmann machine [15]. Both studies show much better results on classification compared to the other studies using classical feature extraction methods. While the amount of studies on medical image analysis using deep learning is still limited, it has shown that the usage of deep learning might help scientists to move from the problem of segmentation of MRI data to more important subjects such as brain disease diagnosis by using the resulted segmentation.

For the immediate future, getting a good result in WMH segmentation is not enough in the study of AD. Developing an automatic WMH segmentation is important, but diagnosing and predicting the progression of AD is more substantial. Just imagine a case where we can predict AD's progression for the next following years when we have a set of consecutive years of data from one AD patient as long as we have a good way to do automatic segmentation and quantification of AD's WMH from those data. This case should be the future of the medical image analysis. Some methods to do such thing, trying to simulate the evolution of lesions over time, have been studied before for analyses of MRI of tumors [16]. I believe that having a similar approach for AD would be of great benefit not only for the study of AD but also for planning assisted care of AD patients in the future.

References

[1] John Hardy. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. Journal of Alzheimer's Disease, 9:151–153, 2006.

[2] Béatrice Duthey. Background paper 6.11: Alzheimer disease and other dementias. A Public Health Approach to Innovation, pages 1–74, 2013.

[3] Valdés Hernández, Zoe Morris, David Alexander Dickie, Natalie A Royle, Susana Munoz Maniega, Benjamin S Aribisala, Mark E Bastin, Ian J Deary, and Joanna M Wardlaw. Close correlation between quantitative and qualitative assessments of white matter lesions. Neuroepidemiology, 40(1):13–22, 2013.

[4] Susanne G Mueller, Michael W Weiner, Leon J Thal, Ronald C Petersen, Clifford R Jack, William Jagust, John Q Trojanowski, Arthur W Toga, and Laurel Beckett. Ways toward an early diagnosis in alzheimer's disease: the alzheimer's disease neuroimaging initiative (adni). Alzheimer's & Dementia, 1(1):55–66, 2005.

[5] Rhoda Au, Joseph M Massaro, Philip A Wolf, Megan E Young, Alexa Beiser, Sudha Seshadri, Ralph B D'Agostino, and Charles DeCarli. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham heart study. Archives of neurology, 63(2):246–250, 2006.

[6] Adam M Brickman, Frank A Provenzano, Jordan Muraskin, Jennifer J Manly, Sonja Blum, Zoltan Apa, Yaakov Stern, Truman R Brown, José A Luchsinger, and Richard Mayeux. Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident alzheimer disease in the community. Archives of neurology, 69(12):1621–1627, 2012.

[7] JA Luchsinger, AM Brickman, C Reitz, SJ Cho, N Schupf, JJ Manly, MX Tang, SA Small, R Mayeux, C DeCarli, et al. Subclinical cerebrovascular disease in mild cognitive impairment. Neurology, 73(6):450–456, 2009.

[8] Massimo Filippi, Maria A Rocca, Nicola De Stefano, Christian Enzinger, Elizabeth Fisher, Mark A Horsfield, Matilde Inglese, Daniel Pelletier, and Giancarlo Comi. Magnetic resonance techniques in multiple sclerosis: the present and the future. Archives of neurology, 68(12):1514–1520, 2011.

[9] Prastawa M, Bullitt E, Moon N, Van Leemput K, Gerig G. Automatic Brain Tumor Segmentation by Subject Specific Modification of Atlas Priors. Academic radiology. 2003; 10(12):1341-1348.

[10] Martijn D. Steenwijk, Petra J.W. Pouwels, Marita Daams, Jan Willem van Dalen, Matthan W.A. Caan, Edo Richard, Frederik Barkhof, Hugo Vrenken, Accurate white matter lesion segmentation by k nearest neighbor classification with tissue type priors (kNN-TTPs), NeuroImage: Clinical, Volume 3, 2013, Pages 462-469, ISSN 2213-1582, http://dx.doi.org/10.1016/j.nicl.2013.10.003.

[11] Vamsi Ithapu, Vikas Singh, Christopher Lindner, Benjamin P Austin, Chris Hinrichs, Cynthia M Carlsson, Barbara B Bendlin, and Sterling C Johnson. Extracting and summarizing white matter hyperintensities using supervised segmentation methods in alzheimer's disease risk and aging studies. Human brain mapping, 35(8):4219–4235, 2014.

[12] Mariana Leite, Letícia Rittner, Simone Appenzeller, Heloísa Helena Ruocco, and Roberto Lotufo. Etiology-based classification of brain white matter hyperintensity on magnetic resonance imaging. Journal of Medical Imaging, 2(1):014002, 2015.

[13] Stefan Klöppel, Ahmed Abdulkadir, Stathis Hadjidemetriou, Sabine Issleib, Lars Frings, Thao Nguyen Thanh, Irina Mader, Stefan J Teipel, Michael Hüll, and Olaf Ronneberger. A comparison of different automated methods for the detection of white matter lesions in mri data. NeuroImage, 57(2):416–422, 2011.

[14] Mohammad Havaei, Axel Davy, David Warde-Farley, Antoine Biard, Aaron Courville, Yoshua Bengio, Chris Pal, Pierre-Marc Jodoin, Hugo Larochelle. Brain Tumor Segmentation with Deep Neural Networks. CoRR: abs/1505.03540. 2015.

[15] Heung-Il Suk, Seong-Whan Lee, Dinggang Shen, Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis, NeuroImage, Volume 101, 1 November 2014, Pages 569-582, ISSN 1053-8119, http://dx.doi.org/10.1016/j.neuroimage.2014.06.077.

[16] I. Rekik, S. Allassonnière, T. Carpenter, J. Wardlaw. Medical image analysis methods in MR/CT-imaged acute-subacute ischemic stroke lesion: Segmentation, prediction and insights into dynamic evolution simulation; NeuroImage: Clinical 1(1) 164-178 (2012). PMCID: PMC3703431.