NeuroImage: Clinical 18 (2018) 638–647

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

DEWS (DEep White matter hyperintensity Segmentation framework): A fully automated pipeline for detecting small deep white matter hyperintensities in migraineurs

Bo-yong Park[a,b,1], Mi Ji Lee[c,1], Seung-hak Lee[a,b], Jihoon Cha[d], Chin-Sang Chung[c], Sung Tae Kim[e], Hyunjin Park[b,f,*]

[a] Department of Electronic, Electrical and Computer Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea
[b] Center for Neuroscience Imaging Research, Institute for Basic Science (IBS), Suwon, 16419, Republic of Korea
[c] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 06351, Republic of Korea
[d] Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul, 03722, Republic of Korea
[e] Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 06351, Republic of Korea
[f] School of Electronic and Electrical Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea

ARTICLE INFO

Keywords:
Deep white matter hyperintensity
Automated detection
Migraine

ABSTRACT

Migraineurs show an increased load of white matter hyperintensities (WMHs) and more rapid deep WMH progression. Previous methods for WMH segmentation have limited efficacy to detect small deep WMHs. We developed a new fully automated detection pipeline, DEWS (DEep White matter hyperintensity Segmentation framework), for small and superficially-located deep WMHs. A total of 148 non-elderly subjects with migraine were included in this study. The pipeline consists of three components: 1) white matter (WM) extraction, 2) WMH detection, and 3) false positive reduction. In WM extraction, we adjusted the WM mask to re-assign misclassified WMHs back to WM using many sequential low-level image processing steps. In WMH detection, the potential WMH clusters were detected using an intensity based threshold and region growing approach. For false positive reduction, the detected WMH clusters were classified into final WMHs and non-WMHs using the random forest (RF) classifier. Size, texture, and multi-scale deep features were used to train the RF classifier. DEWS successfully detected small deep WMHs with a high positive predictive value (PPV) of 0.98 and true positive rate (TPR) of 0.70 in the training and test sets. Similar performance of PPV (0.96) and TPR (0.68) was attained in the validation set. DEWS showed a superior performance in comparison with other methods. Our proposed pipeline is freely available online to help the research community in quantifying deep WMHs in non-elderly adults.

1. Introduction

Migraine is neurological disorder affecting ~20% of people worldwide. While it is believed that migraine is a benign disease, the risk of stroke, cardiovascular diseases, and death is increased in migraineurs (Kurth et al., 2016). Migraineurs show an increased load of white matter hyperintensities (WMHs) and more rapid WMH progression than migraine-free controls (Erdélyi-Bõtor et al., 2015; Kruit et al., 2004; Palm-Meinders et al., 2012). In addition, common psychiatric comorbidities of migraine such as depression and increased suicidality are also associated with increased WMH load (Herrmann et al., 2008; Serafini et al., 2011). A vascular hypothesis is commonly proposed as a possible pathophysiology underlying deep WMH development, while the development of periventricular WMH is currently more debated (Fazekas et al., 1993; Fernando et al., 2006).

WMHs have been linked to several neurological disorders such as vascular cognitive impairment. WMHs are also prevalent in the healthy population, which has led to debate on the clinical importance of WMHs in asymptomatic subjects (Mineura et al., 1995). However, recent studies have shown that WMHs are associated with an increased risk of cognitive decline, incident dementia, ischemic stroke, and death in asymptomatic healthy subjects (Debette and Markus, 2010; Murray et al., 2010; Vermeer et al., 2003). While the causative role of WMH for these conditions is still considered controversial, these findings may indicate that WMH can be a marker of brain damage, warranting more research on their development in earlier life.

* Corresponding author at: Center for Neuroscience Imaging Research/School of Electronic and Electrical Engineering, Sungkyunkwan University, Suwon, 16419, Republic of Korea.
E-mail address: hyunjinp@skku.edu (H. Park).

[1] Equal contribution as co-first authors.

https://doi.org/10.1016/j.nicl.2018.02.033
Received 28 October 2017; Received in revised form 10 February 2018; Accepted 28 February 2018
Available online 02 March 2018

As first suggested by Fazekas et al., WMHs have been classified into periventricular and deep WMHs (Fazekas et al., 1987). Risk factors and clinical implications differ between the two types of WMHs (Griffanti et al., 2017; Kim et al., 2008). In the CAMERA-2 study, women with migraine had a higher incidence and progression of deep WMHs, while such an association was not found for periventricular WMHs (Palm-Meinders et al., 2012). Longitudinal studies demonstrated that the progression of periventricular WMH is associated with a decline in cognitive function and cerebral blood flow, while no such association was found with deep WMHs (Seo et al., 2012; ten Dam et al., 2007; Van Dijk et al., 2008). Different pathogeneses may be involved in the development of periventricular and deep WMHs (Kim et al., 2008). Autopsy studies suggested that deep WMHs were of hypoxic/ischemic origin, while periventricular WMHs seldom showed markers of ischemia. Periventricular WMHs are strongly related to advanced age and arterial hypertension, but this association is weaker for deep WMHs (Griffanti et al., 2017). Taken together, deep WMHs might be more relevant to migraine and its ischemic complications than periventricular WMHs.

Currently available methods for automated quantification of WMH are less robust in the segmentation of small, juxtacortical deep WMHs (Griffanti et al., 2017). In previous studies on WMH segmentation, only elderly subjects with a high load of both periventricular and deep WMHs were recruited (Griffanti et al., 2016; Jeon et al., 2011; Klöppel et al., 2011; Yoshita et al., 2006). However, in young healthy subjects, WMHs are often discrete, small-sized, and located in the deep white matter (Hopkins et al., 2006). Therefore, accuracy of the detection of small, superficially-located WMHs has not been adequately evaluated in the literature. Furthermore, a simple intensity-based thresholding technique has been widely used to detect WMHs in previous studies (Hulsey et al., 2012; Ithapu et al., 2014; Jeon et al., 2011; Klöppel et al., 2011). However, this technique is not optimal for detection of small or low-intensity WMHs because lowering the threshold of WMH segmentation increases the rate of false-positives. In addition, this technique might underestimate superficially-located deep WMHs due to the similar intensities between gray matter (GM) and WMHs (Jeon et al., 2011). However, when examining WMHs among young healthy individuals, it is crucial to detect small, relatively low-intensity, and superficially-located deep WMHs, which have been difficult to identify to date. To overcome the limitations of previous detection methods, several characteristics of deep WMHs, such as intensity value, shape, and location should be considered.

In the current study, we developed a new, fully-automated, machine learning-based pipeline for detecting deep WMHs, DEWS (DEep White matter hyperintensity Segmentation framework), using non-elderly migraineurs. For accurate detection of small, superficially-located deep WMHs, we established a new procedure for WM mask extraction and a classification model based on size, texture and multi-scale deep features as well as intensity threshold information.

2. Materials and methods

The proposed pipeline of this study consisted of three components: 1) WM extraction, 2) WMH detection, and 3) false positive (FP) reduction. The overall scheme of our pipeline is given in Fig. 1.

2.1. Participants and imaging data

We prospectively collected magnetic resonance imaging (MRI) data of new patients diagnosed with migraine at the Samsung Medical Center headache clinic from January 2015 to January 2017. The diagnosis of migraine was confirmed by two headache specialists (MJL and C-SC) based on the International Classification of Headache Disorders-3rd edition beta version (ICHD-3 beta) (Headache Classification Committee of the International Headache Society [IHS], 2013). We included patients with 1.1 migraine without aura, 1.2.1 migraine with typical aura, and 1.3 chronic migraine. A total of 233 non-elderly patients aged ≤ 65 who voluntarily underwent brain MRI during the study period were considered eligible for the analysis. After reviewing all MRI data, we excluded 67 subjects with motion-related artifacts and 18 subjects who did not have deep WMHs in their MRI scan. Finally, 148 subjects were enrolled in the study. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center. Written consent was waived by the IRB.

The T1-weighted and fluid attenuated inversion recovery (FLAIR) MRI scans were acquired using a 3 Tesla MR scanner (Achieva, Philips Medical Systems, Best, Netherlands). The imaging parameters of T1-weighted data were as follows: repetition time (TR) = 9.9 ms; echo time (TE) = 4.6 ms; field of view (FOV) = 240 × 240 mm^2; acquisition matrix = 480 × 480 pixels; and slice thickness = 1 mm with 360 slices. The imaging parameters of the FLAIR data were as follows: TR = 11,000 ms; TE = 125 ms; inversion time = 2800 ms; FOV = 240 × 240 mm^2; acquisition matrix = 512 × 512 pixels; and slice thickness = 2 mm with 80 slices. The same MRI scanner and protocol were applied for all subjects during the study period.

2.2. Manual annotations of WMHs

The manual annotations of deep WMHs were drawn on the 2D slice of FLAIR images by two investigators (MJL, a neurologist with 8 years of experience in clinical neurology, and JC with 11 years of experience in neuroradiology) who were blinded to the clinical information. WMHs were defined as a round- or oval-shaped FLAIR hyperintensity with a variable size in the U-fiber or subcortical WM, which can be discrete or confluent and showed T1 iso- or hypo-intensity (Wardlaw et al., 2013). WMHs were carefully differentiated from subcortical infarctions, perivascular spaces, and artifacts (Kwee and Kwee, 2007; Wardlaw et al., 2013). Periventricular WMHs and lacunes in deep nuclei were excluded from the manual annotations. Periventricular WMH was defined as hyperintensities along the walls of ventricles with an appearance of small caps, thin rims, or confluent lesions (Fazekas et al., 1987; van den Heuvel et al., 2006). The intra-class correlation coefficient between the two raters was 0.994 (95% confidence interval between 0.968 and 0.999) for the number of WMHs for each subject.

2.3. WM extraction

The overall processing was performed using AFNI, FSL, and MATLAB (Cox, 1996; Jenkinson et al., 2012). The T1-weighted and FLAIR data were reoriented to the right-posterior-inferior (RPI) direction and the T1-weighted data were registered onto the FLAIR data using rigid body transformation. The magnetic field bias for both the T1-weighted and FLAIR data was corrected and the skull was removed (Fig. 1A). The T1-weighted data were segmented into GM, WM, and cerebrospinal fluid (CSF) using FSL (Fig. 1A). However, due to the similar intensities between WMH and GM, some voxels of the WMH were misclassified to GM. The following steps were performed to adjust the WM mask to include WMH voxels. The segmented WM mask was dilated and eroded in the axial plane (both x and y directions) with disk size of 5 voxels to fill the holes (shown in yellow circles) in the WM mask which were due to the misclassified WMH voxels (Fig. 1B). The segmented GM mask was adjusted by multiplying the GM partial volume effect (PVE) mask with the complement (i.e., logical negative) of the WM mask of the previous step. The adjusted GM mask was dilated in the axial plane with a disk size of 2 voxels (Fig. 1B). The segmented CSF mask was skeletonized and dilated in the axial direction with a disk size of 6. The ventricle mask was extracted from the segmented CSF mask using the region growing method in each slice. The ventricle mask was dilated in all three directions with a sphere radius of 5 voxels to remove potential periventricular WMHs and MRI induced artifacts near the ventricle which could be misjudged as periventricular WMHs (Fig. 1B). The deep brain structures of the hippocampus, amygdala,