Multi-atlas based detection and localization (MADL) for location-dependent quantification of white matter hyperintensities

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Abstract

The extent and spatial location of white matter hyperintensities (WMH) on brain MRI may be relevant to the development of cognitive decline in older persons. Here, we introduce a new method, known as the Multi-atlas based Detection and Localization (MADL), to evaluate WMH on fluid-attenuated inversion recovery (FLAIR) data. This method simultaneously parcellates the whole brain into 143 structures and labels hyperintense areas within each WM structure. First, a multi-atlas library was established with FLAIR data of normal elderly brains; and then a multi-atlas fusion algorithm was developed by which voxels with locally abnormal intensities were detected as WMH. At the same time, brain segmentation maps were generated from the multi-atlas fusion process to determine the anatomical location of WMH. Areas identified using the MADL method agreed well with manual delineation, with an interclass correlation coefficient of 0.97 and similarity index (SI) between 0.55 and 0.72, depending on the total WMH load. Performance was compared to other state-of-the-art WMH detection methods, such as BIANCA and LST. MADL-based analyses of WMH in an older population revealed a significant association between age and WMH load in deep WM but not subcortical WM. The findings also suggested increased WMH load in selective brain regions in subjects with mild cognitive impairment compared to controls, including the inferior deep WM and occipital subcortical WM. The proposed MADL approach may facilitate location-dependent characterization of WMH in older individuals with memory impairment.

1. Introduction

White matter hyperintensities (WMH) that appear on T2-weighted or fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) are a common radiological feature. WMH are primarily thought to reflect the degree and distribution of small vessel disease (wardlaw et al., 2013), and they are increasingly common with advancing age (debette and markus, 2010; Gorelick et al., 2011; Prins and Scheltens, 2015). Recent findings suggest they may also be one of the core features of Alzheimer's disease (AD) (brickman, 2013; Lee et al., 2016), in addition to gray matter atrophy (Vemuri and Jack, 2010).

Several studies have suggested that it might be important to consider the spatial distribution of WMH when evaluating individuals with memory impairment. For example, periventricular WMH (pwWMH) are more strongly associated with cognitive performance than deep WMH (dWMH) (de groot et al., 2002; de carli et al., 2005), and posterior WMH was shown to play an important role in the development of AD (Lee et al., 2016; Yoshita et al., 2006). Hypothesis-driven investigation of WMH in other brain regions were also reported (biesbroek et al., 2013; Brickman et al., 2012; Brickman et al., 2015; Murray et al., 2016; Wu et al., 2006). These findings suggest the importance of developing tools that not only measure the total WMH load but also systematically evaluate the WMH distribution, e.g., WMH load in different lobular divisions and various subcortical structures.

Fully automated WMH detection algorithms have been developed over the past decade, including various forms of intensity-based thresholding methods (admiral–Behloul et al., 2005; Jack et al., 2001; Ji et al., 2013; Ong et al., 2012; Simoes et al., 2013; yoo et al., 2014), clustering approaches (ithapu et al., 2014; Lao et al., 2008; Seghier et al., 2008), outlier analysis methods (maldjian et al., 2013; Ong et al., 2012; van leemput et al., 2001; Yang et al., 2010), morphological operations...
is the posterior probability of voxel $p_l(x) \mid I$ that WMH voxel have abnormal intensities that do not comply with the intensity profile of label $\lambda$.

$\pi = 1 \times 1\, \text{mm}$, 69 slices with slice-thickness of 2 mm. T1-weighted images were acquired with a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with TI/TE/TR = 800/3/7 ms, flip angle of 8°, FOV of $256 \times 256 \times 204$ mm, and resolution of $1 \times 1 \times 1\, \text{mm}$.

### 2.2. FLAIR multi-atlas generation

A FLAIR multi-atlas library was created with FLAIR data from cognitively normal individuals who had minimal WMH (< 1.2 ml based on manual delineation). Seventeen images qualified for this criterion, but two had slight image artifacts, and therefore 15 images were chosen as atlases. The demographic and basic clinical information of the atlas data matched with the test data (Table 1), and the 15 atlases represented a range of anatomy from minimal to moderate degrees of brain atrophy (Fig. 1A).

The 15 FLAIR images were first registered to T1-weighted images of the same brains in Montreal Neurological Institute (MNI) coordinates, by maximizing the mutual information between the FLAIR and T1-weighted images using the SPM package in Matlab (mathworks.com). The T1-weighted images were then segmented into 283 regions of interest (ROIs) (Wu et al., 2016) using a multi-atlas segmentation pipeline established by the investigators (Tang et al., 2013) (Wu et al., 2016). This way, the registered FLAIR data were segmented into the same 283 ROIs. For the purposes of this study, we manually edited the segmentations on FLAIR images, and regrouped the finest level of ROIs based on their ontological relationships. In the end, 143 ROIs were defined in FLAIR atlases. Of these, there were 24 WM ROIs (Fig. 1B) used in the following analyses, and the rest were ROIs for gray matter (GM), cerebrospinal fluid (CSF) and non-brain tissue. The WM ROIs were included in the analyses below (see Fig. 2A).

### 2.3. MADL for WMH detection

To identify WMH, the MADL algorithm takes advantage of the fact that WMH voxels have abnormal intensities that do not comply with the local intensity profiles of the ROIs where they reside, resulting in low posterior probabilities in the multi-atlas fusion process. The algorithm flowchart is depicted in Fig. 2.

1) Global inhomogeneity correction on the target image (image to be segmented) was performed using N4 bias correction (Tustison et al., 2010), followed by histogram matching (Coltuc et al., 2006) between the target and atlas images. Atlas images were transformed to the target image first through affine registration and then non-linear transformation, using a method known as large deformation diffeomorphic metric mapping (LDDMM) (Christensen et al., 1996; Grenander and Miller, 1998).

2) Atlas-weighting and fusion were performed based on a multi-atlas likelihood fusion method, in which voxelwise posterior probabilities were derived through

$$\bar{p}(l \mid x, I_T) = \sum_{i=1}^{N} w_i(l) \cdot p(l \mid x, I_A^i)$$

(1)

where $\bar{p}(l \mid x, I_T)$ is the posterior probability of voxel $x$ in target image $I_T$ being assigned to label $l (l \in \{1, \ldots, L\})$; $I_A^i$ ($i \in \{1, \ldots, N\}$, $N$ being the number of atlases) are the warped atlas images; $w_i(l)$ is the atlas-weighting term determined iteratively by the spatial matching between the atlas label and the target label derived in the previous iteration; and $p(l \mid x, I_A^i)$ is the prior likelihood determined by the Gaussian probability density of voxel intensity at location $x$ of the target image with respect to the intensity profile of label $l$ in the atlas image $I_A^i$ (Tang et al., 2013). Voxels with abnormal intensities will give low prior likelihood with respect to the corresponding label.

3) Anatomical labels are obtained using Bayes maximum a posteriori (MAP) estimation:

Table 1

| Participant characteristics | Data used as atlases | Data used in algorithm evaluation and diagnostic analysis |
|----------------------------|----------------------|--------------------------------------------------------|
| Number of participants     | 15 (all)             | Normal MCI                                             |
| Age in years (mean ± SD)   | 70.1 ± 8.3           | 70.0 ± 8.5, 69.9 ± 8.7                                  |
| Gender (% female)          | 73%                  | 64%, 59%                                               |
| MMSE (mean ± SD)           | 29.6 ± 0.8           | 29.5 ± 0.8, 27.6 ± 2.0                                 |

$^* p < .001$ difference in MMSE between normal and MCI groups.
where $L_T$ is the final label image. At the same time, the maximum posterior probability (MPP) $\beta(L_T | x, I_T)$ is obtained at each voxel.

4) WMH voxels are identified as voxels with low MPP values below a threshold. The threshold was empirically optimized based on comparison with manually delineated WMH labels. The effect of the choice of threshold was evaluated.

Fig. 1. The FLAIR multi-atlas library. (A) Images of 6 of the 15 FLAIR atlases that represented a range of anatomy from to minimal to moderate degrees of brain atrophy. (B) Major WM structures defined in the FLAIR atlases. Abbreviations: dWM—deep white matter; sWM—subcortical white matter; BCC—body of corpus callosum; GCC—genus of corpus callosum; SCC—splenium of corpus callosum; ALIC—anterior limb of internal capsule; PLIC—posterior limb of internal capsule.

Fig. 2. Flowchart of the MADL pipeline. A multi-atlas library of FLAIR images is used to segment the brain and generate the posterior probability map based on a multi-atlas likelihood fusion algorithm. WMH voxels are detected if the maximum posterior probabilities are below a threshold, within a WM mask. Normalized image intensity was applied to exclude voxels with low intensities. Regional WMH load is obtained based on the simultaneously generated segmentation map and WMH label.
5) Post-processing. Several steps are taken to reduce the false positive

detection.

i) A WM mask is generated using a simplified parcellation map (WM, GM, CSF, lateral ventricle, etc.) (Ma et al., 2015), using the same
multi-atlas segmentation framework. Voxels outside the WM mask
are removed.

ii) Because the MADL algorithm detects local intensity abnormalities, voxels with abnormally low intensities are also detected, e.g., CSF
voxels (dark on FLAIR) that are encapsulated in cortical ROIs. Therefore, we applied an intensity threshold to exclude dark voxels
lower than 1.5 standard deviations below the mean ROI intensity.

iii) After the above two steps, WMH clusters with volume below 50 mm³ are removed.

2.4. Algorithm evaluation

1) WMH detection accuracy was evaluated based on manually deli-
neated WMH labels by a board certified neurosurgeon (Y.T.), who is
experienced in brain MRI analysis. The delineation was performed in ROIEditor (mristudio.org) using manually selected seeds, followed by region growing and manual editing. The following eval-
uation metrics were used.

i) The Dice similarity index (DSI, \( \frac{2TP}{2TP + FP + FN} \)), false-positive rate (FPR, \( \frac{FP}{TP + FP} \)), and false-negative rate (FNR, \( \frac{FN}{TP + FN} \)) (Griffanti et al., 2016) were calculated between the WMH labels detected with MADL and the manual labels in each subject. The DSI, FPR, and FNR were evaluated in three groups of individuals with low (< 5 ml, n = 75), median (5–10 ml, n = 34), and high (> 10 ml, n = 15) WMH load in the entire brain. Representative WMH maps of low, median, and high load brains are shown in Fig. 3C.

ii) WMH volume correspondence between the MADL and manual re-
sults was evaluated using interclass correlation (ICC) with the
consistency agreement definition (McGraw and Wong, 1996).

iii) Receiver-operating characteristic (ROC) curves were calculated using voxelwise false-positive detection rate versus true-positive rate, based on which the area under the ROC curve (AUC) was calculated in each subject.

2) We compared the MADL outputs with two state-of-the-art WMH
detection algorithms: (a) the Brain Intensity Abnormality Classification Algorithm (BIANCA) (Griffanti et al., 2016), which employs user-provided training data to classify abnormal intensities with a k-nearest neighbor algorithm and is implemented in FSL (Isl.fmrib.ox.ac.uk/isl/fslwiki/BIANCA), and (b) the Lesion Segmentation Toolbox (LST, version 2.0.15), as implemented in SPM12 (https://www.applied-statistics.de/lst.html). We used the lesion prediction algorithm (LPA) (Schmidt; 2017) in LST, which was trained by a logistic regression model with internal training data.

For BIANCA, WMH probability maps were generated in a leave-one-
out fashion (recursively, 119 of the 120 FLAIR data with manually delineated WMH were used as training data for the remaining test image). An empirical threshold of 0.9 and a cluster size of 10 was used to obtain WMH labels from the probability maps, as suggested by (Griffanti et al., 2016). For LST, WMH probability maps were generated with its internal training data, and we used a recommended probability threshold of 0.5 to obtain WMH labels. DSI, FPR, FNR, and ICC were used to evaluate the BIANCA and LST results.

2.5. Application of algorithm to clinical data

To examine the utility of MADL based WMH identification, we in-
vestigated the relationship between local WMH load and (i) the
participant age and (ii) the clinical diagnosis. All statistical analyses
were performed in R (www.r-project.org). Significance was detected at a
5% false discovery rate (FDR) after correcting for multiple comparisons
(Benjamini and Hochberg, 1995). WMH ROIs used in this analysis
are listed in Table 3. Note that the left and right sides of the corpus
callosum (CC) were combined in the statistical analyses, resulting in
three ROIs for the CC—the genu, body, and splenium parts (GCC, BCC, and SCC, respectively). In addition, the anterior and posterior limbs of
the internal capsule were not included in the analysis since they did not
show WMH in most subjects.

1) Relationships between age, WMH load, and WM volumes of
individual ROIs were assessed with linear regressions, including (a)
regressions between age and local WMH load (log-transformed), and
(b) regressions between age and WM structural volumes. Regression
analyses were adjusted for clinical diagnosis and sex, and corrected
for multiple comparisons.

2) Group differences in local WMH load between the cognitively
normal and MCI participants were assessed by analysis of covariance
(ANCOVA), adjusted for age and sex and corrected for multiple
comparison. Due to the unbalanced sample size between normal and
MCI groups (n = 98 versus n = 22), we used type ANCOVA with
type II sum of squares (Langsrud, 2003).

3. Results

3.1. Performance of the MADL pipeline

3.1.1. Effect of thresholding

We evaluated the detection accuracy at different MPP thresholds, and voxels with MPP below the threshold were detected as WMH. DSI and ICC were calculated in the low (< 5 ml), median (5–10 ml), and high (> 10 ml) groups based on the total WMH load (Fig. 3C). The effect of thresholding was relatively small in the range of 0.01–0.05 (Fig. 4A), except that the DSI of the low WMH group slightly decreased as the threshold increased above 0.03. An MPP threshold of 0.02 was used in the following analysis.

3.1.2. Comparison with manual detection

The whole-brain WMH load (in unit of ml) detected with the MADL
pipeline showed a high level of agreement with manual delineation,
with an ICC of 0.97 across 120 subjects (Fig. 3A). Majority of the par-
ticipants in this study demonstrated a low-to-median amount of WMH,
and the ICC was 0.89 in a sub-population with WMH < 20 ml (dashed
area in Fig. 3A). ROC curve of the voxelwise detection accuracy is
shown in Fig. 3B, with an overall AUC of 0.89 ± 0.05. AUCs in the low,
median, and high WMH groups were 0.89 ± 0.05, 0.89 ± 0.03, and
0.85 ± 0.04, respectively. DSI, FPR, and FNR measurements in low,
median, and high WMH groups are reported in Table 2. DSI increased
and FPR/FNR decreased as the total WMH load increased. The overall
DSI, FPR, and FNR of the entire study population were 0.62 ± 0.09,
0.35 ± 0.14, and 0.37 ± 0.12, respectively, given that 88% of the
study population were in the low and median groups.

3.1.3. Comparison with other algorithms

We compared the performance of the MADL, BIANCA, and LST,
based on DSI, FPR, and FNR in the low, median, and high WMH groups and ICC of the entire population. Table 2 shows that the highest ICC
was obtained using MADL, and the DSI were similar among the three
methods, using pairwise t-tests (all p > .05). BIANCA showed the
highest FPR and lowest FNR, and LST showed the lowest FPR and
highest FNR, among the three methods (p < .01 by paired t-tests be-
tween MADL and BIANCA and between MADL and LST).
3.2. Relationship between location-dependent WMH and age

Whole-brain WMH load (log-scaled) was significantly correlated with age \( (r = 0.36, \ p < .01) \). The association between age and WMH load was significant in most of the deep WM (dWM) ROIs, including the bilateral posterior dWM, bilateral occipital dWM, left frontal dWM, and SCC \( (r = 0.24–0.43, \ p < .05) \), but not in the subcortical WM (sWM), after FDR multiple comparison correction (Table 3 and Fig. 5A). The \( r \) value maps in Fig. 5C depict a central-to-peripheral pattern for the accumulation of WMH with age.

WM volumes were negatively correlated with several regions, including the bilateral parietal sWM, bilateral temporal sWM, right frontal sWM, bilateral anterior dWM, left posterior dWM, and right inferior dWM \( (p < .05 \) after FDR correction) (Table 2 and Fig. 5B). Fig. 5D demonstrates that age-dependent volume loss was more prominent in peripheral WM structures, which is opposite to the pattern of age-WMH relationships observed in Fig. 5C.

3.3. Relationship between location-dependent WMH and diagnosis

We also compared local WMH load in participants who were cognitively normal \( (n = 98) \) versus participants who had a diagnosis of MCI \( (n = 22) \). Significant group differences were found in the right inferior dWM, and left occipital sWM \( (p < .05) \), based on ANCOVA, adjusted for age and sex and corrected for multiple comparisons (Fig. 6A). No statistical group difference was found in the whole-brain WMH loads \( (p = .06) \). An example of the WMH distribution in an MCI subject is shown in Fig. 6C. Visual inspection indicated that WMH (red arrows in Fig. 6C) often crossed the inferior dWM and occipital sWM. Therefore, we further combined these two ROIs, and found significant differences in both left and right inferior-occipital WM regions between the normal and MCI groups \( (p < .05) \). The WM volumetric analysis revealed significant group differences in bilateral temporal sWM, after adjusting for age and sex and correcting for multiple comparison (Fig. 6B).

4. Discussion

4.1. The MADL framework

The new MADL algorithm seamlessly integrates WMH detection and image segmentation to quantify the WMH distribution. The method was built on a multi-atlas fusion algorithm and FLAIR multi-atlas library. While multi-atlas algorithms are traditionally used for segmenting images, we utilized the multi-atlas fusion process for WMH detection purpose. The MADL method can be considered as a special case of outlier detection. While previous outlier detection methods (Maldjian et al., 2013; Ong et al., 2012; Van Leemput et al., 2001; Yang et al., 2010) utilized the intensity profiles within the patient images; whereas MADL identifies outliers based
interclass correlation (ICC) and the Dice Similarity Index (DSI), in three groups (whole-brain WMH load of 0–5 ml, 5–10 ml, and > 10 ml).

(B) MADL results at threshold of 0.01, 0.03, and 0.05 in a brain at two transverse locations. Red arrows point to the increase of true-positive detection as the threshold increased; and yellow arrows point to the increase of false-positive detection as the threshold increased.

Table 2
Performance of MADL, BIANCA, and LST in detecting WMH, using manually delineated WMH as the gold standard.

| Method | Load  | DSI      | FPR   | FNR   | ICC  |
|--------|-------|----------|-------|-------|------|
| MADL   | 0–5 ml| 0.55 ± 0.09 | 0.42 ± 0.17 | 0.37 ± 0.16 | 0.97 |
|        | 5–10 ml| 0.64 ± 0.07 | 0.29 ± 0.11 | 0.33 ± 0.09 |      |
|        | > 10 ml| 0.72 ± 0.05 | 0.19 ± 0.09 | 0.31 ± 0.08 |      |
| BIANCA | 0–5 ml| 0.55 ± 0.14 | 0.55 ± 0.18 | 0.22 ± 0.17 | 0.95 |
|        | 5–10 ml| 0.67 ± 0.12 | 0.39 ± 0.14 | 0.21 ± 0.15 |      |
|        | > 10 ml| 0.74 ± 0.05 | 0.26 ± 0.07 | 0.22 ± 0.08 |      |
| LST    | 0–5 ml| 0.53 ± 0.19 | 0.27 ± 0.21 | 0.52 ± 0.24 | 0.94 |
|        | 5–10 ml| 0.66 ± 0.12 | 0.22 ± 0.17 | 0.41 ± 0.21 |      |
|        | > 10 ml| 0.73 ± 0.09 | 0.17 ± 0.09 | 0.32 ± 0.13 |      |

The dice similarity index (DSI), false positive rate (FPR), and false negative rate (FNR), were evaluated in low, median, and high WMH groups. Intra-class correlation (ICC) was calculated based on the detected and the manual delineated total WMH load in all subjects (n = 120), using the three methods.

4.2. Algorithm performance

MADL algorithm showed a comparable detection accuracy compared to the state-of-the-art methods, and its performance was robust with respect to the choice of MPP thresholds. The accuracy of WMH detection algorithms varied depending on the amount of WMH in the brain. Using single-modality FLAIR contrast, DSI was between 0.51 and 0.71 in the subjects with < 5 ml WMH load, and overall accuracy was about 0.68 in previous reported fully-automated methods (Gibson et al., 2010; Ji et al., 2013; Khademi et al., 2012; Schmidt et al., 2012; Simoes et al., 2013; Yoo et al., 2014). Higher detection accuracy can be achieved with semi-automated methods (Iorio et al., 2013; Itti et al., 2001; Kawata et al., 2010; Ramirez et al., 2011). When compared directly using the same dataset, MADL, BIANCA, and LST showed similar DSI. Interestingly, the FPR was the highest in BIANCA and lowest in LST, and the FNR was the highest in LST and lowest in BIANCA, while MADL was intermediate (Table 2). There are several reasons why the outcomes of these algorithms may differ. BIANCA is a supervised learning method based on k-nearest neighborhood clustering, with user-defined options for spatial weighting, local intensity averaging, and choice of training points (Griffanti et al., 2016). In addition, the empirically defined threshold on the lesion probability map played an important role in balancing the FPR and FNR. We used a suggested threshold of 0.9 and default values for other parameters, which might not be optimal for our study population with relatively low WMH load. By comparison, the LPA algorithm (Schmidt, 2017) in LST was trained by a logistic regression model based on internal training data from multiple sclerosis patients with severe lesions. Given the intrinsic differences in lesion volume and pattern between the LPA training data and our testing data, it is possible that the algorithm is not sensitive enough to capture the small and subtle lesions in our data, leading to the high FNR.

Detection accuracy in the low load group was not ideal with all three methods. Small lesions with subtle abnormalities are known to be challenging for fully automated algorithms. Even human readers show considerable disagreement and inconsistency on detection of small lesions (Boutet et al., 2016). It is, therefore, recommended that visual inspection, parameter tuning, and manual correction are performed after automated detection. Another source of detection error resides in the ambiguity of WMH definition. WMH are commonly used to examine...
Table 3

Correlation coefficients ($r$) between age and log-scale WMH load and those between age and WM volumes in major WM structures, as well as the total WMH load (in the unit of ml) in normal elderly and MCI patients in these structures.

| White matter structure | $r$ between age and WMH load | $r$ between age and volumes | WMH (ml) in normal elderly | WMH (ml) in MCI patients |
|------------------------|-----------------------------|-----------------------------|---------------------------|--------------------------|
| Anterior dWM (left)    | 0.26*                       | $-0.37^{**}$                | 0.28 ± 0.41               | 0.35 ± 0.47              |
| Anterior dWM (right)   | 0.09                        | $-0.37^{**}$                | 0.20 ± 0.29               | 0.28 ± 0.40              |
| Posterior dWM (left)   | 0.34**                      | $-0.28^{*}$                 | 0.06 ± 0.14               | 0.10 ± 0.27              |
| Posterior dWM (right)  | 0.43**                      | 0.15                        | 0.04 ± 0.09               | 0.12 ± 0.28              |
| Inferior dWM (left)    | 0.39**                      | $-0.17$                     | 0.14 ± 0.23               | 0.24 ± 0.37              |
| Inferior dWM (right)   | 0.24*                       | $-0.23^{*}$                 | 0.10 ± 0.16               | 0.25 ± 0.40              |
| Frontal sWM (left)     | 0.15                        | $-0.14$                     | 0.02 ± 0.03               | 0.01 ± 0.02              |
| Frontal sWM (right)    | 0.06                        | $-0.19^{*}$                 | 0.03 ± 0.08               | 0.01 ± 0.03              |
| Parietal sWM (left)    | 0.06                        | $-0.32^{**}$                | 0.03 ± 0.05               | 0.03 ± 0.07              |
| Parietal sWM (right)    | 0.26                       | $-0.43^{**}$                | 0.02 ± 0.04               | 0.02 ± 0.05              |
| Temporal sWM (left)    | 0.01                        | $-0.28^{**}$                | 0.00 ± 0.01               | 0.00 ± 0.00              |
| Temporal sWM (right)    | 0.09                       | $-0.25^{*}$                 | 0.01 ± 0.03               | 0.02 ± 0.04              |
| Occipital sWM (left)   | 0.19                        | $-0.13$                     | 0.08 ± 0.09               | 0.15 ± 0.20              |
| Occipital sWM (right)   | 0.11                        | $-0.16$                     | 0.08 ± 0.10               | 0.13 ± 0.19              |
| Genu of CC              | 0.02                        | $-0.12$                     | 0.08 ± 0.05               | 0.09 ± 0.06              |
| Body of CC              | 0.17                        | 0.17                        | 0.14 ± 0.09               | 0.18 ± 0.12              |
| Splenium of CC          | 0.28**                      | 0.01                        | 0.14 ± 0.19               | 0.21 ± 0.22              |

$^*$p < .05 and $^{**}$p < .01 after adjustment for gender and diagnosis and correction for multiple comparison. Abbreviations: dWM—deep white matter, sWM—subcortical white matter, CC—corpus callosum.

Fig. 5. Relations between WMH load, structural volume, and age. Linear regressions in structures that had significant correlations between their WMH and age (A) and between their volumes and age (B) are shown. Three-dimensional maps of the Pearson's correlation coefficients ($r$) between local WMH load and age (C), and between WM volumes and age (D) are also shown. Abbreviations: dWM, deep white matter; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; SCC, splenium of the corpus callosum; sWM, subcortical white matter.
brain changes associated with small vessel disease, where most hyper-intense voxels reside in WM, but lesions can also appear in GM (Wardlaw et al., 2013). The GM lesions could also be important but whether or not they should be detected by algorithms designed for WMH is controversial. In MADL, we only characterized lesions within a WM mask. However, our manual WMH delineation included lesions in both GM and WM. If we only use manual delineation within the WM mask as the gold standard, agreement between the MADL and manual results were higher, e.g., DSI can be improved to 0.59 ± 0.08, 0.66 ± 0.08, and 0.71 ± 0.04 in the low, median, and high load groups.

It should be noted that in the current MADL pipeline, we selected 15 FLAIR data for the multi-atlas library, which were from cognitively normal subjects with normal-appearing images and minimal WMH. Previous studies have reported that performance of T1-weighted multi-atlas segmentation improved with the number of atlases, but segmentation accuracy became relatively stable between 15 and 25 atlases, depending on the structures of interest (Aljabar et al., 2009). We examined the effect of atlas number by expanding the original 15 atlases to 20 atlases with brains that had WMH < 2ml. We compared algorithm performance in a randomly selected subset of subjects (n = 22). The detection accuracy was not affected by atlas number: DSI was 0.65 ± 0.08 using 20 atlases, and 0.66 ± 0.08 using 15 atlases (p > .05 by paired t-test).

4.3. Significance of location-dependent WMH analysis

To examine the clinical use of the location-dependent WMH analysis by MADL, we first investigated WMH accumulation with advancing age. The location-dependent WMH analysis demonstrated that local WMH was significantly correlated with age in the dWM regions, while age-volume correlations were more prominent in the sWM. We also examined the location dependency of WMH distribution in normal elderly subjects compared to those with MCI. The association between WMH and AD has been reported in a number of studies (Barber et al., 1999; Burns et al., 2005; Prins et al., 2004; Vermeer et al., 2003), and MCI subjects tend to have an intermediate WMH burden (Yoshita et al., 2006). In our study, whole-brain WMH load was marginally different between cognitively normal and MCI participants, but we were able to identify significant local WMH increases in the inferior dWM and occipital sWM in MCI subjects, which is congruent with previous reports (Brickman et al., 2012; Yoshita et al., 2006). It remains to be demonstrated whether WMH load and WM atrophy can be used synergistically in identification of MCI. Although the WMH remains an incremental and non-specific feature in many neurodegenerative diseases (Wardlaw et al., 2013), our results suggested the value of examining the locations of WMH in subjects with memory impairment. The current study did not investigate associations between WMH and cognitive performances or other clinical factors, which will be an interesting clinical research topic to explore but outside the scope of the current study.

4.4. Limitations and future directions

The present study represents the initial phase of WMH lesion-detection techniques based on multi-atlas approaches; many interesting challenges remain. For example, ROI definitions in the FLAIR atlases were inherited from T1-weighted anatomical definitions, which could be optimized according to the characteristics of WMH distribution, e.g., by merging some of the ROIs, to facilitate clinical interpretation. In the current pipeline, histogram matching between subjects and atlases was performed based on the whole brain intensity profiles, which might be affected by the abnormal intensities in WMH regions. While this was not a particular concern for our study population who had low-to-median WMH load, for patients with extensive WMH, such as vascular dementia patients, it might be necessary to first exclude the WMH regions in histogram matching to ensure the accuracy of image registration, which would, in turn, improve the segmentation and detection of large WMH.
A few more strategies may also be attempted to further improve the performance of MADL. For example, one may explicitly use WMH probability information obtained from existing subjects as a prior to refine the MADL detection results, similar to (Bricq et al., 2008; Yoshita et al., 2006). Another natural extension of the technology is to combine multiple MR contrasts (e.g., T1-weighted images), into a multi-contrast multi-atlas approach to further improve detection and segmentation accuracy. Within the FLAIR image contrast, additional features beyond the intensity may be utilized, including the first and second order features from texture analysis (Haralick et al., 1973), Haar-like features that enhance edge and shape information (Lienhart and Maydt, 2002), context information (Torralba et al., 2003), or even features learned from radiomics (Gillies et al., 2016) or machine-learning. These high-order image features may assist the detection of small lesions with subtle intensity abnormalities. Also, the boundaries of hyperintense regions, which were subject to partial volume effects, may be better captured by incorporating graph-cut (Shi and Malik, 1997) or level-set (Chan and Vese, 2001) algorithms.

In addition, recent advances in deep learning have opened a new avenue for medical image analysis, including WMH detection (Ghafoorian et al., 2016; Ghafoorian et al., 2017; Jin et al., 2018; Moeskops et al., 2018; Roa-Barco et al., 2018). For example, using a fully-connected convolutional neural network (CNN) with multiple branches, Moeskops et al. showed that WMH can be segmented jointed with GM/WM/CSF with DSI around 0.54 using three image contrasts and DSI of 0.51 using only FLAIR (Moeskops et al., 2018). Rachmadi and colleagues reported that the segmentation accuracy of CNN also depended on the WMH load, e.g., for small-to-medium size WMH (1.5-13 ml), DSI was between 0.46 and 0.55, and it was increased to 0.72 for very large WMH (> 24 ml). In the 2017 MICCAI Challenge of WMH segmentation (http://wmh.isi.uu.nl/), deep learning based methods were among the top performers, which achieved DSI above 0.7 using TI-weighted and FLAIR images in patients with presumed vascular disease. Potential integration of deep learning and traditional image processing algorithms may strengthen the advantages of both and fundamentally improve the performance of image segmentation and lesion detection.

5. Conclusion

The multi-atlas based method provided a one-stop-shop solution for simultaneous detection and localization of WMH on FLAIR data. This method demonstrated good detection accuracy compared with manual delineation and other existing methods. The location-dependent WMH analysis suggested a higher association between deep WMH and age compared to subcortical WMH. Our findings also suggested that WMH may differentially accumulate in the inferior and occipital WM during the MCI phase of AD.

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None of the authors have a conflict of interest to declare.

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