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Computer-aided detection of cerebral microbleeds in susceptibility-weighted imaging

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ABSTRACT

Susceptibility-weighted imaging (SWI) is recognized as the preferred MRI technique for visualizing cerebral vasculature and related pathologies such as cerebral microbleeds (CMBs). Manual identification of CMBs is time-consuming, has limited reliability and reproducibility, and is prone to misinterpretation. In this paper, a novel computer-aided microbleed detection technique based on machine learning is presented: First, spherical-like objects (potential CMB candidates) with their corresponding bounding boxes were detected using a novel multi-scale Laplacian of Gaussian technique. A set of robust 3-dimensional Radon- and Hessian-based shape descriptors within each bounding box were then extracted to train a cascade of binary random forests (RF). The cascade consists of consecutive independent RF classifiers with low to high posterior probability constraints to handle imbalanced training sets (CMBs and non-CMBs), and to progressively improve detection rates. The proposed method was validated on 66 subjects whose CMBs were manually stratified into "possible" and "definite" by two medical experts. The proposed technique achieved a sensitivity of 87% and an average false detection rate of 27.1 CMBs per subject on the "possible and definite" set. A sensitivity of 93% and false detection rate of 10 CMBs per subject was also achieved on the "definite" set. The proposed automated approach outperforms state of the art methods, and promises to enhance manual expert screening. Benefits include improved reliability, minimization of intra-rater variability and a reduction in assessment time.

1. Introduction

Cerebral microbleeds (CMBs) represent small foci hemosiderin deposition in normal brain tissue, corresponding to prior microscopic hemorrhages [1]. CMBs are relatively small in size (few millimeters), appear spherical and hypointense on magnetic resonance images (MRI), and are becoming recognized as important imaging findings in cognitive impairment and dementia [2], stroke and intracerebral haemorrhages [3] and cerebral amyloid angiopathy [4].

Manual localization and counting is the gold standard technique to assess the incidence of CMBs. This is a challenging task, as it is extremely time-consuming, subjective, and has high inter-expert variability [5]. Moreover, visual screening is prone to errors as small CMBs can be easily missed, or mistaken for vessel cross-sections, especially in MR susceptibility-weighted imaging (SWI). SWI is a 3D flow-compensated T2* gradient echo which maximizes the sensitivity of susceptibility effects by combining filtered phase information with magnitude information [6]. SWI has several advantages over T2* gradient-recall echo for detecting CMBs, such as 2 to 6-folds increased sensitivity in CMB detection [7,8], and enhanced the resolution of smaller lesions (i.e. less than 1 mm in diameter) [7]. Furthermore, to improve inter-rater agreement, established rating scales have separated CMBs into two categories: *definite* and *possible* [9]. Definite CMBs, which are defined spherical with enough hypointensity, have been widely considered in clinical studies and assessments [10], since they increase detection

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Table 1
Table below summarizes the performance of the proposed method and other published computer-aided microbleed detection approaches on both Possible and Definite CMBs.

Method	MRI modality	Mag. field	Pathology	# of subjects	# of CMBs	Sensitivity	Ave. FPs
Ref. [11]	T2*	1.5 T	Stroke	30	114	50%	–
Ref. [12]	SWI	1.5 T	AD/MCI	6	126	81.7%	107
Ref. [13]	T2*	7.0 T	CerbVa[a]	18	66	71.2%	17.2
Ref. [14]	SWI	3.0 T	Tumor	10	304	86.5%	44.9
Ref. [5]	T2*	3.0 T	AD/MCI	38[b]	148	78%	49
Proposed method	SWI	3.0 T	AD/MCI	66	231	87.0%	27.1

AD, Alzheimer's disease; MCI, mild cognitive impairment; CMB, cerebral microbleeds; SWI, susceptibility-weighted imaging; FP, false-positive.
[a] CerbVa: cerebrovascular disease.
[b] From a total of 72 subjects just 38 were confirmed with CMBs.

confidence [9]. For instance, it has been suggested to exclude individuals with 2 or more definite CMBs (using SWI) from amyloid-modifying therapeutic trials due to the potential of adverse drug events [10].

To aid manual CMB assessments and eventually supplant them with automatic approaches, advanced computer vision and image analysis approaches have been investigated [11–14,5]. These studies implemented a two-step method consisting of an automated pre-screening to identify all CMB-like regions, followed by a high-level detection model to refine falsely detected regions. However, these methods suffered from a high false detection rate and low sensitivity as summarized in Table 1. The pre-screening is designed to achieve a high sensitivity at the cost of specificity due to the diverse appearance of both CMBs and surrounding structures seen on MRI. In the second step, machine learning techniques have not been well explored compared to the rule-based or statistical approaches. However, such a technique may face an imbalanced classification problem since the low-level pre-screening identifies large number of non-CMB regions (majority class) compared to true CMBs (minority class). In such cases, conventional classifiers tend to perform poorly [15], though, it has been demonstrated that random sampling with bagging or boosting strategies have the highest performance in large and imbalanced datasets [16].

This paper presents a novel computer-aided technique for detecting cerebral microbleeds in SWI, particularly aimed at achieving a high sensitivity with a low false detection rate. The proposed technique is comprised of three main steps. First, a low-level automated pre-screening scheme based on a multi-scale Laplacian of Gaussian (LoG) is performed to detect potential CMBs (candidates), with the ultimate goal of achieving a high sensitivity leaving almost no true CMBs behind, but at the cost of increased candidates. Second, a 3D bounding box proportional to the size of the central hypointensity is defined for each candidate, and subsequently robust Radon and Hessian shape feature descriptors which are invariant to scale, rotation, translation and intensity shift are computed. To tackle the class imbalance problem for classification, the third step employs a cascade of consecutive binary random forest (RF) classifiers to progressively reduce the training sample size (false detections) throughout the cascade and reach a high detection accuracy. The overview of the proposed method is shown in Fig. 1.

The novelties of the proposed approach are in the following areas: (i) identifying spherical shapes and their extent through a novel multi-scale Laplacian of Gaussian (LoG) technique, and (ii) addressing the class imbalance issue by incorporating a series of binary RF classifiers with low to high posterior probability constraints. Unlike [17,18], the proposed multi-scale LoG approach is adapted for MR images especially with anisotropic resolutions which cause some CMBs to appear relatively semi-spherical or ovoid in shape. Furthermore, the modified Laplacian operator response is capable of detecting of CMBs adjacent to vessels and sulcus folding. The multi-layer classifier approach in contrast to [19,20] not only handles class imbalance problem in an efficient way using several RF classifiers, but it also provides a flexible framework to obtain a desirable sensitivity/specificity by extending the number of layers, and updating a single parameter (posterior probability) at each layer.

2. Materials and methods

2.1. Dataset

Data used in the preparation of this paper were obtained from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study [21]. The 66 participants included 11 subjects classified as Alzheimer's Disease (AD), 14 as mild cognitive impairment (MCI) and 41 healthy controls (HC). The subjects included 27 females (age 77.9 ± 7.7, mean $\pm$ std) and 39 males (age 71.9 ± 6.6).

All subjects underwent an anatomical T1-weighted (T1w) and a SWI acquisitions on a 3T Siemens TRIO scanner, where SWIs were automatically reconstructed online using the scanner system (software VB17). The 3D SWIs were acquired with 0.93 mm $\times$ 0.93 mm in-plane resolution and 1.75 mm slice thickness, repetition time/echo time of 27/20 ms, and flip angle 20°. T1w images were acquired using a standard 3D magnetization-prepared rapid gradient echo sequence with in-plane resolution 1.0 mm $\times$ 1.0 mm, slice thickness 1.2 mm, repetition-time/echo-time/T1 = 2.300/2.98/900, flip angle 9°, field of view 240 $\times$ 256, and 160 slices.

SWIs were manually inspected for CMBs by two clinical experts using the MARS rating method [9], labeling CMBs as *definite* and

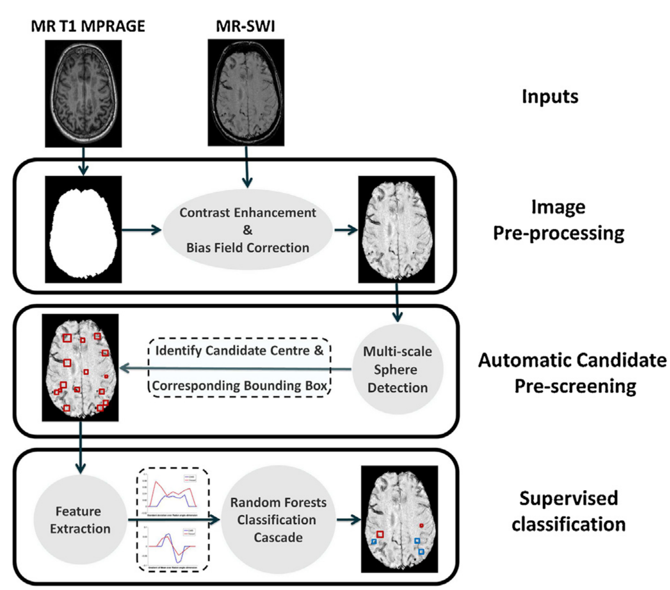

Fig. 1. Overview of the proposed processing pipeline.