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Computer-aided detection of radiation-induced cerebral microbleeds on susceptibility-weighted MR images

Wei Bian [a,b], Christopher P. Hess [b], Susan M. Chang [c], Sarah J. Nelson [a,b,d,*], Janine M. Lupo [b]

[a] The UC Berkeley & UCSF Graduate Program in Bioengineering, University of California San Francisco, San Francisco, CA, USA
[b] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA
[c] Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA
[d] Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA

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ABSTRACT

Recent interest in exploring the clinical relevance of cerebral microbleeds (CMBs) has motivated the search for a fast and accurate method to detect them. Visual inspection of CMBs on MR images is a lengthy, arduous task that is highly prone to human error because of their small size and wide distribution throughout the brain. Several computer-aided CMB detection algorithms have recently been proposed in the literature, but their diagnostic accuracy, computation time, and robustness are still in need of improvement. In this study, we developed and tested a semi-automated method for identifying CMBs on minimum intensity projected susceptibility-weighted MR images that are routinely used in clinical practice to visually identify CMBs. The algorithm utilized the 2D fast radial symmetry transform to initially detect putative CMBs. Falsely identified CMBs were then eliminated by examining geometric features measured after performing 3D region growing on the potential CMB candidates. This algorithm was evaluated in 15 patients with brain tumors who exhibited CMBs on susceptibility-weighted images due to prior external beam radiation therapy. Our method achieved heightened sensitivity and acceptable amount of false positives compared to prior methods without compromising computation speed. Its superior performance and simple, accelerated processing make it easily adaptable for detecting CMBs in the clinic and expandable to a wide array of neurological disorders.

1. Introduction

Cerebral microbleeds (CMBs) are small, frequently perivascular collections of brain parenchymal hemosiderins induced by prior hemorrhage. On MR T2*-weighted gradient echo (GRE) magnitude images, CMBs appear as small, rounded, hypointense lesions of variable size due to susceptibility-related signal loss within iron-containing hemosiderins that accumulate paramagnetic ferric atoms (Charidimou and Werring, 2011; Cordonnier et al., 2007; Greenberg et al., 2009). Since the susceptibility effect scales linearly with magnetic field strength, the contrast of CMBs is greatly enhanced by higher field strengths (e.g., at 3 T or 7 T) and susceptibility-weighted imaging (SWI) (Ayaz et al., 2010; Conijn et al., 2011; Nandigam et al., 2009). Because this heightened contrast has facilitated the detection of CMBs, there is a growing interest in exploring their diagnostic and prognostic values in diseases such as cerebral amyloid angiopathy (CAA) (Greenberg et al., 1999), stroke (Cordonnier et al., 2007; Fiehler, 2006; Werring et al., 2005); neurodegenerative disorders (Cordonnier and van der Flier, 2011), traumatic brain injury (TBI) (Scheid et al., 2003), and radiation therapy-induced injury in patients with gliomas (the most common brain tumors) (Lupo et al., 2012). Although their putative role in neurocognitive function and implications for clinical management are still being evaluated (Charidimou and Werring, 2011; Cordonnier et al., 2007; Greenberg et al., 2009), there is accumulating evidence that CMBs reflect the severity of microvascular damage in the brain due to microangiopathy (Vernooij et al., 2008), TBI (Scheid et al., 2003), or radiation therapy (Lupo et al., 2012).

Visual inspection of CMBs on MR images is especially difficult due to their small size (with radii often <2 mm for radiation-induced CMBs) and wide distribution throughout the brain. In CAA and following cranial radiation, the sheer large number of CMBs can render manual lesion counting impractical or impossible. Detection is further confounded by the presence of normal anatomical structures with heightened magnetic susceptibility that mimic the appearance of CMBs on T2*-sensitive sequences, such as deoxyhemoglobin-containing intracranial veins.

* Corresponding author at: UCSF-Mission Bay, Byers Hall, Room BH-303, MC 2532, 1700 4th Street San Francisco, CA 94158-2330, United States. Tel.: +1 415 476 6383; fax: +1 415 514 1028.
E-mail address: sarah.nelson@ucsf.edu (S.J. Nelson).

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These characteristics make the identification of CMBs a lengthy and arduous task that is prone to human error and substantial intra-rater and inter-rater variability (Cordonnier et al., 2009; Gregoire et al., 2009). An automatic, computer-aided CMB detection method that can both minimize the burden of visual inspection and improve the accuracy of detection of CMBs is therefore highly desirable.

Several methods have been proposed for CMB detection (Barnes et al., 2011; Kuijf et al., 2012; Seghier et al., 2011). Seghier et al. (2011) implemented an intensity-based statistical classification algorithm in which T2*-weighted magnitude images are first registered to a standard template that maps voxelwise probabilities of individual brain structures such as gray matter, white matter, cerebral spinal fluid, and CMBs. Gaussian mixture modeling is then applied to distinguish CMBs from other brain structures. They identified patients with CMBs at a sensitivity of 77% and a detection rate of 50% for total true CMBs without giving the number of false positives. Barnes et al. (2011) proposed a technique for intensity-based local statistical thresholding that assumes the Gaussian distribution of background tissue in a small region and then identifies hypointense CMBs as outliers. False positives were reduced by constructing a support vector machine that incorporates shape, size and intensity as features for each hypointense region to distinguish CMBs from mimics. They achieved a detection sensitivity of 81.7% with 107.5 false positives per patient. Kuijf et al. (2012) developed an algorithm for CMB detection based on the fast radial symmetry transform (FRST), which enhances local objects with spherical or near-spherical geometry (Loy and Zelinsky, 2003). By using the transform, the algorithm achieved a detection rate of 71.2% with 17.2 false positives per patient.

Despite the reported success of these computer-aided methods for detecting CMBs, there remains a need to improve diagnostic accuracy with simpler processing, less computation time, and greater robustness in the presence of anatomic distortion such as brain tumors, resections, and infarcts. In addition, all of the above methods are designed to detect CMBs on T2*-weighted magnitude or SWI images without minimum intensity projection (mIP) processing, which helps distinguish CMBs from hypointense veins and is used in clinical practice for visual inspection of CMBs (Lupo et al., 2012), even by the groups who have developed these automated methods (Ayaz et al., 2010; de Bresser et al., in press). Direct adaptation of their methods for CMB detection on mIP images may be nontrivial as the original geometric coordinates and characteristics of CMB vary after the mIP process, rendering some of the prerequisites associated with these features invalid for these methods.

In this study, we propose a new approach for CMB detection with higher sensitivity and faster computation than has been previously reported, even in the presence of anatomic disease. This approach aims to detect CMBs on mIP SWI images, and the detection process is divided into two main steps: 1) initial putative CMB detection using the 2D FRST, 2) subsequent false positive reduction by characterizing geometric features of putative CMBs through region growing. Although the FRST has already been used to detect CMBs on T2*-weighted magnitude images (Kuijf et al., 2012), the transform was performed in 3D, which requires isotropic image acquisition, and even a perfectly spherical paramagnetic object under isotropic acquisition becomes elongated along the direction of the main magnetic field on T2*-weighted images because the profile of its perturbation of the external field is not spherical (Schenck, 1996). Also, the transform has been modified and utilized in new ways in our implementation. To illustrate the effectiveness of the proposed approach, we applied the method to a series of patients with CMBs induced by radiation treatment for resected gliomas.

2. Methods

2.1. CMB detection algorithm

The proposed algorithm can be divided into two primary steps: 1) identification of putative CMBs using 2D FRST; and 2) false positive reduction of putative CMBs identified in the first step using 3D region growing followed by geometric feature examination. A flowchart depicting the steps for this algorithm is given in Fig. 1. Details of the implementation will be described in the following sections.

2.1.1. Detection of putative CMBs using 2D FRST

2.1.1.1. FRST. The inherently circular morphology of CMBs on SWI images makes lesion geometry an ideal feature for automated detection. For this purpose, a modified version of the FRST that was developed by Loy and Zelinsky (2003) was adopted in our algorithm. Our goal in this initial step was to select a set of parameters that would identify the greatest possible number of true microbleeds, regardless of the number of false positives.

FRST is a gradient-based transform that begins with a computation of the gradient of each pixel using the 3×3 Sobel operator. If a pixel $\mathbf{p}$ lies on the edge of a circular disk, then the direction of its gradient $\mathbf{g(p)}$ is orthogonal to the edge, pointing to (if the circular disk is hyperintense) or away from (if the disk is hypointense) the center of the circle. The pixel that is at a distance n pixel away from $\mathbf{p}$ along the direction of $\mathbf{g(p)}$ is defined as a *positively-affected pixel*, whereas the pixel that is at a distance n pixel away from $\mathbf{p}$ along the direction opposite to that of $\mathbf{g(p)}$ is defined as a *negatively-affected pixel*. Since

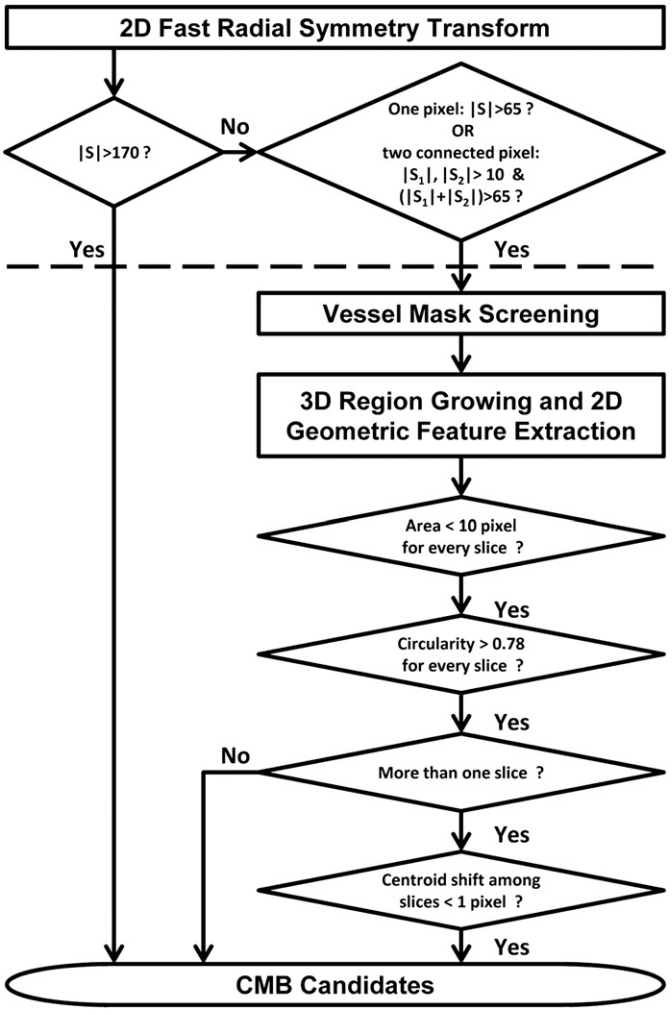

Fig. 1. Schematic diagram for the proposed CMB detection algorithm and selected optimized parameters. (*S* refers to the intensity of FRST map; the processing above the dashed line belongs to the step of initial putative CMB detection, while the below belongs to the step of false positive reduction.)