# Automatic assessment of iron deposits in MR brain images

Maria C. Valdés Hernández, Paul A. Armitage, Joanna M. Wardlaw

Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

**Abstract**. We developed two alternative approaches for segmenting brain microbleeds (BMBs) along with other hemosiderin deposits (HDs) in the brain and differentiating the iron areas from those with prevalence of calcium. One technique uses a multispectral approach based on the fusion of two or more types of structural images registered and modulated in frequency to the red/green colour space, and quantifies the volume of the areas segmented by Minimum Variance Quantization. The other approach consists of a combined thresholding, size and shape analysis using T2*-weighted images, along with information from the corresponding T1-weighted sequence. We tested it using structural MRI data from a sample of 50 participants of the Lothian Birth Cohort 1936. Preliminary results suggest that the techniques are fast, accurate, and show excellent correlation with one another, and with visual classification of HDs. Further validation in a wider range of subjects and with validated rating scales is now underway.

**Keywords:** automatic segmentation, microbleeds, hemosiderin, basal ganglia, calcium, iron, mineralization, MRI, data fusion, minimum variance quantization.

## 1 Introduction

Some forms of microvascular "disease" in the brain are asymptomatic. Mineralization of small blood vessels identified in pathology studies [1] has staining properties of both iron and calcium, but the discrepant sensitivity between neuroimaging modalities (CT vs MRI) and the putative relevance of their reported findings has created confusion regarding their identification and the identification of brain microbleeds (BMBs). The latter are microhaemorrhages identifiable in MR T2*-weighted images by small, homogeneous round foci of low signal intensity. They are considered a biomarker for microangiopathy and provide useful prognostic information for the treatment of stroke. Several studies [2] assess them visually, but to our knowledge there has not been any attempt to extract them automatically and differentiate them from the controversial areas of mineralized vessels. Therefore, we developed two approaches for segmenting hemosiderin deposits (HDs) and mineralized areas in brain MR images.

## 2 Materials and Methods

### 2.1 Subjects

To validate the segmentation methods, 50 elderly subjects were selected with different loads of BMBs and a variety of mineralized areas, both with regard to location and proportion of iron/calcium. The subjects were all healthy older members (age 71-72 years old) of the Lothian Birth Cohort 1936[3]. Subjects were still included if their scans revealed incidental findings, such as old infarcts.

### 2.2 MRI scans

Table 1 illustrates the values of the scan parameters for the T1- (T1W), T2- (T2W), T2*-weighted (T2*W) and FLAIR sequences used in these studies.

**Table 1**. TR/TE times of the structural MRI sequences used.

| Study | T1W | T2W | T2*W | FLAIR |
|---|---|---|---|---|
| | TR/TE (ms) | TR/TE (ms) | TR/TE (ms) | TR/TE (ms) |
| LBC1936 | 9.8/4 | 11320/104.9 | 940/15 | 9002/147.38 |

### 2.3 Multispectral approach : MCMxxxVI(1936)

To apply our technique, we first selected two MR sequences that provide good separability for the pathology of interest, i.e. hemosiderin. Figure 1 shows a section of the T2*W and FLAIR images from a mid-central axial slice in a representative subject. It displays, from left to right, T2*W, its fusion with FLAIR represented in the red/green (RG) space, and the FLAIR image. A BMB is circled. In the fused image it appears in green. Combining two different types of images in the one-dimensional grey-scale space results in loss of information, while, if the fusion is done in the two-dimensional colour space, the information is enhanced.

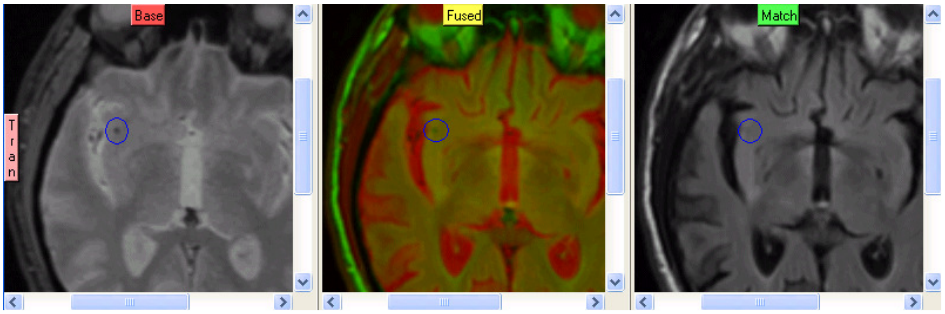


**Fig. 1.** Section of a central axial slice of a subject displaying the registration and colour fusion of T2*W and FLAIR volumes, with a BMB highlighted in the sub-cortical white matter located in the right insula.

Not all combinations can be used to segment HDs. Visual inspection of the different image contrasts available in this study revealed that the coloured combination of T2*/FLAIR is optimum to identify them. Figure 2 shows the combination of T2*W and T1W in another subject. Again, the area where a BMB appears in the basal ganglia is circled. In the right and central images they are not clearly distinguishable.

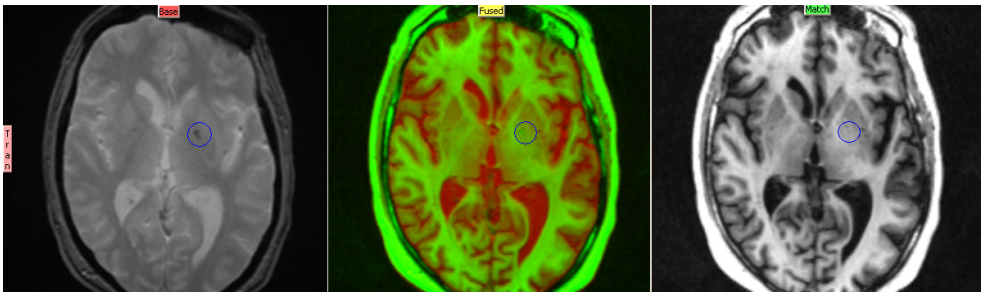


**Fig. 2.** Central axial slice of a subject displaying the registration and colour fusion results of T2*W and T1W, showing a non-mineralised hemosiderin deposit in the basal ganglia.

When HDs are not associated with mineralised areas where calcium is present, fusions based on T1W images do not provide sufficient contrast for segmenting them. However, T1W images are very useful for distinguishing the presence of calcium. Figure 3 shows one slice of a mineralised basal ganglia. The presence of calcium does not change the colour in which the HD areas are identified in the coloured combination of T2*W and FLAIR because both substances appear as low intensity signals in T2*W and low-contrast areas of medium intensity in FLAIR images. But the presence of calcium has an opposing effect on signal intensity in T1W images compared to the hemosiderin, and therefore alters the darkness of the areas on T1W images that contain both minerals. It demonstrates that, in principle, in order to distinguish the presence of calcium associated with the depositions of iron oxyhydroxide in an insoluble form, we could have optimised our technique using 3 different MR images instead of two and modulate them in the red/green/blue (3D) colour space instead. This paper only aims to identify and segment iron deposits, and using only 2 images imposes less restrictions to its practical application.

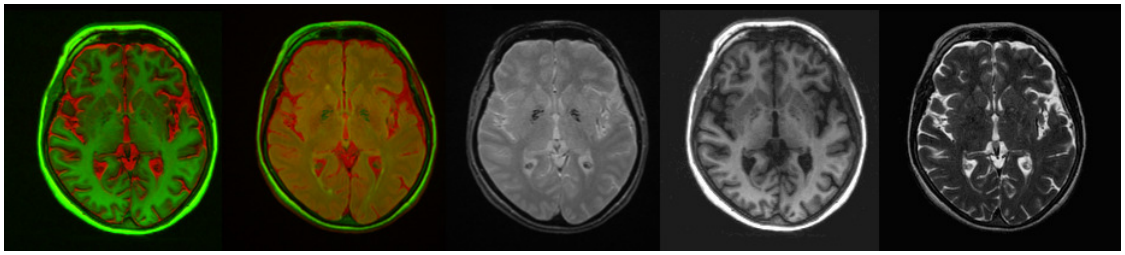

**Fig. 3.** Central axial slice of a subject displaying, from left to right, the registration and fusion results of T2W and T1W, the result of the same process using T2*W and FLAIR images, the correspondent T2*W, T1W and T2 images, showing a mineralised basal ganglia.

The second step was to register the axial volumes. We used FLIRT[4] – a tool from the FMRIB software library that performs affine linear registration. Then, we adjusted the intensity values of the volumes to increase their contrast prior to fusing them to obtain a volume in the RG colour plane (Figure 1). This step guarantees that when we transform the registered images into the hue, saturation and value (HSV) colour space [5] with an angle of 120˚, i.e. red and green colours, the features to be segmented are far enough from the V axis (S=0 for any value of H) and, therefore, the model that sustains this transformation will never become undefined.

The next step was to remove the skull and extract the brain. For this, we used the Object Extraction Tool in Analyze 8.1 [6] which applies thresholding, morphological erosion, dilation, and region growing steps. T2*W images were used to obtain the brain mask and extract the brain of the fused volume, because they offer the best contrast between brain and background, and display better integrity of the brain tissue with the CSF.

To segment and quantify the HD volumes, a minimum variance quantization (MVQ) algorithm using Floyd-Steinberg's error diffusion dither was applied, using the implementation found in the MATLAB function 'rgb2ind'. This was used to convert the fused RG image into a clustered image in the same RG colour space. Work was done to identify the optimum number of clusters needed to achieve the best results, and it was found to be 32. The 32 clusters were mapped in a normalised graph of the RG space. We determined the clusters in the range of green that best identify the hemosiderin areas through interactive sampling. The results of MVQ have been considered [7] better than other clusterisation methods because the actual image colour statistics are taken into account: more colour map entries are allocated to densely populated areas in the colour space, and fewer entries are allocated to infrequent colours, thus achieving higher colour accuracy in the quantized image.

We named this technique, and its software programme: MCMxxxVI. This stands for Multispectral Colouring Modulation and Variance Identification. The name of the method also coincides with the number "1936" represented in roman numerals and reflects the Lothian Birth Cohort 1936 (www.disconnectedmind.org.uk), the project for which this method has been developed.

### 2.4 Thresholding approach

On gradient-echo T2*W MRI, signal loss can represent hemosiderin, calcification, physiological ferritin, melanoma, or air, but not all of them exhibit equal characteristics. The images can be affected by non-pathologically related paramagnetic influences, considered as artifacts (e.g. dentistry), which appear as extended areas of signal ranging from intermediate to low values. However, gradient-echo T2*W images are regarded as a sensitive method for the detection of hemosiderin deposition. Our technique is based on extracting the hypointense areas on T2*W images that satisfy the requirements of maximum size, circularity and threshold range specified according to the characteristics that can be estimated from the image volume under analysis. This process was performed using the 'Object Counter' module in Analyze 8.1 [5]. The first step was to perform an intensity inhomogeneity (bias field) correction by the Guillermaud-Brady filter [8] to minimize the effect of intensity fall-off near the edges of the images. The brain was then extracted, as described previously. Then, a slice was selected where the BMBs or HDs appear, ideally with a variety of shapes and intensities. The intensity threshold was adjusted, starting from zero to less than half of the maximum intensity value, to segment the areas with low intensity. An estimated maximum and minimum size of the hypointensed "objects" was then adjusted interactively. Once the T2*W segmentation is complete, a T1W volume in register can be used to discern the areas where calcium dominates, following the reasoning and principles previously described. The volumetric results obtained were compared with the ones obtained by applying the MCMxxxVI technique.

## 3 Results and Discussion

Both the MCMxxxVI technique and the threshold based method were successfully applied to a wide range of scans with varying noise, pathologies and contrast levels, showing its validity as a tool for clinical use. However, neither segmentation was perfect and both methods required a post-processing step to remove false positive regions. Typical example images and resulting segmentations are illustrated in Fig. 4 and 5 and a screenshot of the MCMxxxVI software tool is shown in Fig. 6.

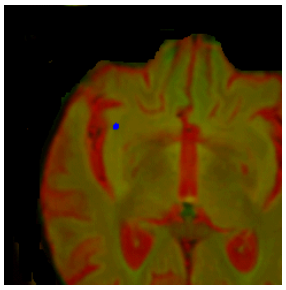

**Fig. 4.** Result of the segmentation of the BMB presented in Fig.1 by MCMxxxVI.

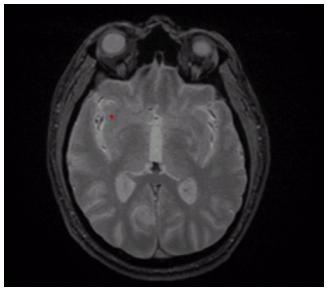

**Fig. 5.** Result of the segmentation of the BMB presented in Fig.1 by thresholding in T2*W images.

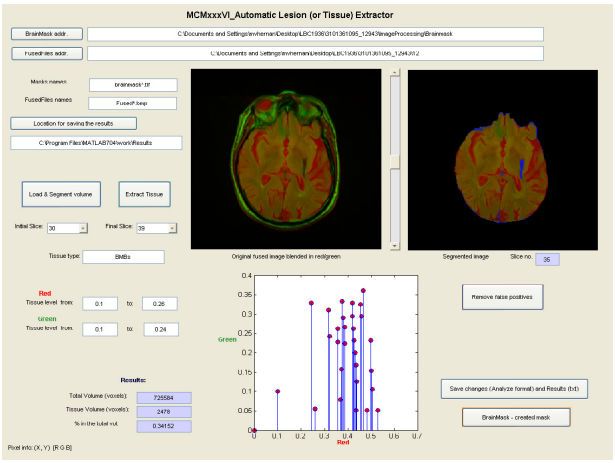


**Fig. 6.** Screen capture of the hemosiderin segmentation by the MCMxxxVI software (left) and results of the correlation coefficient of the sample analyzed by both methods (right).

After segmenting the HDs by both methods in the sample blind to each other, the results were compared. The correlation coefficient between the hemosiderin volumes calculated by both methods was 0.94 (Figure 6). A visual rating scale was also defined to evaluate the results, whereby the iron load was ranked from 1 to 4 according to the extent of visible iron deposit, where 1 represents the lowest amount of iron and 4 the most. Ordered from left to right, Figure 7 illustrates an example of each type. An experienced observer rated the images, blind to all numeric results from the automated methods. The segmented volumes obtained using the quantitative methods corresponded with those from the visual rated scale, showing that both methods are acceptable and in good agreement.

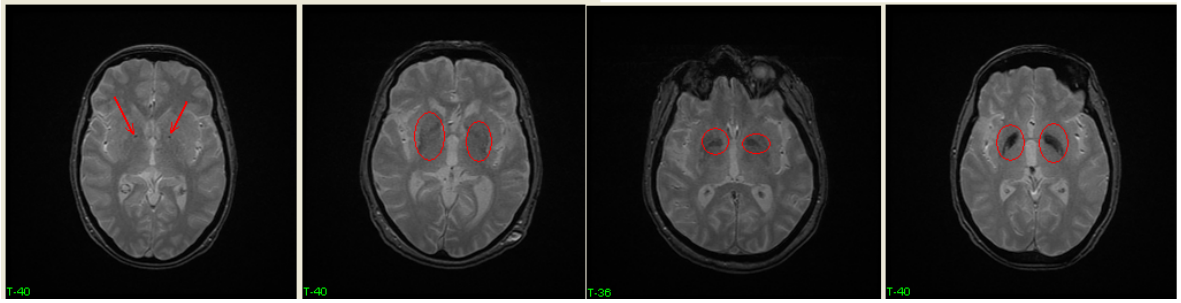

**Fig. 7**. Examples to illustrate the 4 groups of loads of iron in the basal ganglia in T2*W. From left to right: 1 to 4.

## 4 Conclusions

The multispectral fusion method presented here successfully segmented hemosiderin deposits within the brain, with a good correlation obtained between both methods and with visual rating. The method appeared to perform well in the presence of RF inhomogeneities and typical noise levels. We believe this to be the first time that a technique has been developed and applied to the segmentation of hemosiderin deposits and to separate them from the potentially confounding mineralised areas.

The simplicity of the calculations makes both methods fast and accurate. However, both require a post-processing step to remove the false positives identified in the automatic segmentation, and future work aims to reduce the extent to which this is required. Further quantitative validation in a larger number of patients and over wider patient cohorts with expert assessed validated visual rating (such as BOMBS) is now needed.

**Acknowledgements**

The Disconnected Mind is funded by the Help the Aged biomedical Research into Ageing programme and by the Medical Research Council. All MR scanning has being performed in the SFC Brain Imaging Research Centre, University of Edinburgh, UK (www.sbirc.ed.ac.uk/).

**References**

1. Casanova M.F., Araque J.M.: Mineralization of the basal ganglia: implications for neuropsychiatry, pathology and neuroimaging. Psychiatry Research 121, 59-87. (2003)

2. Cordonnier C., Al-Shahi Salman R., Wardlaw J.: Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain . (2007)

3. Deary I.J., Gow A.J., Taylor M.D., Corley J., Brett C., Wilson V., Campbell H., Whalley L.J., Visscher P.M., Porteous D.J., Starr J.M.: The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC Geriatr 7, 28. (2007)

4. Jenkinson M., Bannister P.R., Brady J.M., Smith S.M.: Improved optimisation for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825-841. (2002)

5. Foley JD, van Dam A, Feiner SK, Hughes JF. Computer Graphics: Principles and Practice in C. 2nd. ed. Addison-Wesley Professional; 1996. 1 p.

6. Analyze 8.1. AnalyzeDirect, Inc. Mayo Clinic; 2008.

7. Orchard M.T., Orchard M.T., Bouman C.A.: Color quantization of images. Signal Processing, IEEE Transactions on [see also Acoustics, Speech, and Signal Processing, IEEE Transactions on] 39, 2677-2690. (1991)

8. Guillermaud R., Brady M.: Estimating the bias field of MR images. IEEE Trans on Medical Images 16, 238-251. (1997)