Abnormal brain anatomy can introduce considerable bias to studies relying on FIRST – An improved segmentation pipeline

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TARGET AUDIENCE – Researchers interested in automated brain segmentation.

PURPOSE – Robust and accurate brain image segmentation is required to investigate in large cohort clinical studies variations of MR image intensity or volume of brain structures. Several sophisticated tools have been developed to perform automatic segmentation based on T_1-weighted (T_1w) images. Among them, FMRIB's Integrated Registration and Segmentation Tool (FIRST)[1] is one of the most popular used. However, although these tools aim to segment deep gray matter (DGM) nuclei, the contrast of these nuclei relative to white matter (WM) is generally low on the input T_1w images. Consequently, FIRST often fails to identify tissue boundaries and falls back to the initial guess segmentation. It has recently been demonstrated that this pitfall can be overcome by using a hybrid contrast (HC)[2], created by a weighted combination of T_1w images and quantitative susceptibility maps (QSM)[3], which have an exquisite DGM contrast. Another limitation of FIRST is that it utilizes (by default) FMRIB's Linear Image Registration Tool (FLIRT) to align the input image to the MNI atlas. While linear registration works reasonably well in the case of brain anatomy that is similar to the standard MNI atlas, it is problematic in the case of abnormal anatomy, for example, in neurological diseases with substantial brain atrophy.

In this study we show that the linear registration associated to the standard FIRST pipeline fails in the case of abnormal anatomy, potentially introducing a serious bias to clinical studies. To overcome this issue, we present an improved framework for FIRST segmentation that incorporates both a hybrid contrast generation and a non-linear registration.

METHODS – *Data acquisition:* 11 patients with particularly large or small brain volumes were identified in our local research image database of approximately 2000 healthy subjects and patients with neurological diseases involved in several ongoing studies at our hospital. The local ethics committee approved the experiment and informed written consent was obtained from each recruited subject. T_1w data were acquired with an inversion-recovery prepared spoiled gradient echo sequence (SPGR) using the following sequence parameters: FOV=256x256mm^2, TE=2.8ms, TR=5.9ms, TI=900ms, FA=10°, isotropic voxel size of 1 mm^3. Acquisition parameters of the fully-flow compensated 3D gradient echo acquisition used for QSM were: 64 slices, 0.5x1x2 mm^3 voxel size, 12° flip angle, TE/TR = 22/40ms; 13.89 kHz BW, 8:46 min:sec. The data were acquired on a 3T whole-body GE scanner (Signa Excite HD 12.0; GE Healthcare, Milwaukee, Wisconsin). *Data processing:* All the data were processed on the same computer with Intel Core i7 processor and 24 GB memory. The signal intensities of the T_1w images were normalized so that the white matter (WM) had an intensity centered on 110. GRE data were converted to susceptibility maps (QSM) by employing sophisticated harmonic artifact reduction for phase data (SHARP)[6] and homogeneity enabled incremental dipole inversion (HEIDI)[7].

Proposed pipeline: We created HC images with a contrast similar to the MNI template by combining T_1w images and susceptibility maps as reported previously[2]. Then, we non-linearly registered HC images to the MNI atlas using Advanced Normalization Tools (ANTs)[4] and applied FIRST (without the FLIRT module). We decided to use ANTs because it was shown to deliver the most consistent and accurate registration results among 14 different methods[5]. Finally, we inversely warped the segmented ROIs to the original space of input images. The flowchart of the proposed framework is illustrated in **Figure 1**. *Analysis*: We applied both the default FIRST pipeline and the proposed new pipeline to all subjects. The segmentation results from the two methods were qualitatively (visually) and quantitatively compared to each other. Visual assessment was performed by overlaying the outline of the obtained ROIs over the corresponding DGM structures and assessing if it visually matched with the boundary of the corresponding DGM structures. Quantitative analysis was performed by assessing mean susceptibility values in the ROIs.

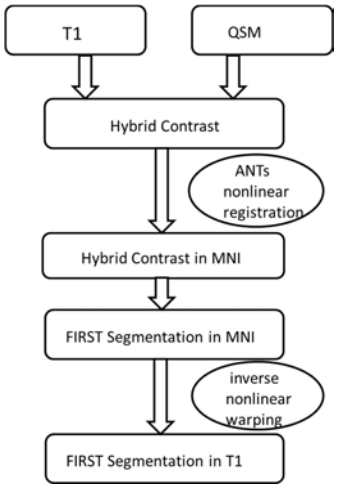

FIGURE 1. Flowchart of the proposed image segmentation framework.

RESULTS – The default FIRST pipeline completed the segmentation in only 8 of the 11 subjects and failed for the 3 subjects, producing no segmentations at all (aborted). Using the proposed pipeline, segmentation successfully completed for all subjects. Visual assessment of the segmentations resulting from the default FIRST revealed that only 2 of the 8 subjects were segmented properly, whereas all other segmentations were located completely wrong. Using the new pipeline appropriate segmentation was obtained in all cases. **Figure 2** illustrates the improvement of segmentation in a representative dataset with brain atrophy, showing enlarged ventricles. **Figure 3** summarizes the susceptibility analysis, showing mean value and standard deviation for each DGM structure over all subjects. Using the new method, more reasonable mean values and smaller standard deviations were obtained, compared to the default method.

DISCUSSION – Our results show that abnormal anatomy results in failure of the default FIRST segmentation pipeline. This may introduce considerable bias in clinical studies. To minimize bias, manual quality checks of all segmentations have to be performed and the segmentation, if failed, has to be carried out manually. The proposed approach overcomes both the limited DGM contrast on T_1w images and the insufficient registration in the default FIRST pipeline in the case of abnormal brain anatomy. The proposed technique does not require any modifications of the actual segmentation algorithm (FIRST) or its training data, because it is solely based on pre- and post-processing of the input images and the results, respectively. To achieve robust and accurate segmentation, the computation costs have increased significantly, from approximate 5 min to more than 3 hours for one subject using the same computation hardware, which mainly comes from the nonlinear registration part. Future improvements may involve a reduction of running time, especially for the case of large-cohort clinical study.

CONCLUSION – Abnormal brain anatomy can introduce considerable bias to studies relying on automatic FIRST segmentation. The presented new segmentation approach overcomes this limitation.

REFERENCES – [1] Patenaude B et al., 2011. *NeuroImage*. 56(3):907-22. [2] Schweser F et al., 2014. *Proc. ISMRM*. 22:1787. [3] Deistung A et al., 2013. *NeuroImage*. 65:299-314. [4] Avants B et al., 2011. *NeuroImage*. 54:2033-044. [5] Klein A et al., 2009. *NeuroImage*. 46(3):786-802. [6] Schweser F et al., 2011. *NeuroImage*. 54(4):2789-807. [7] Schweser F et al., 2012. *NeuroImage*. 62(3):2083-100.

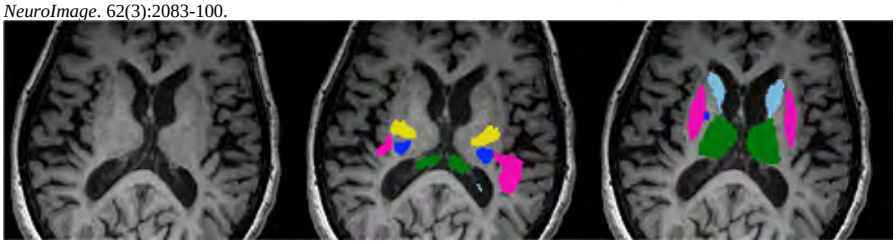

FIGURE 2. Segmentation results overlaid on the corresponding T1 image of a representative subject with brain atrophy. **Left**: The original T1 image. **Middle**: Default FIRST segmentation based on the T1 image. Segmentation failed due to abnormal brain anatomy. **Right**: Segmentation result using the proposed method.

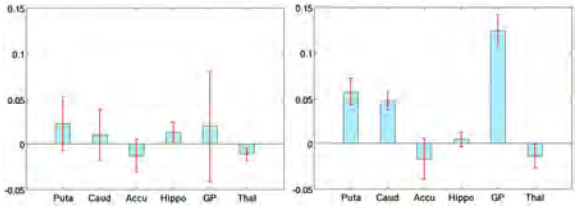

FIGURE 3. Quantitative susceptibility analysis based on the available segmentation results in all 11 subjects. **Left**: Using default FIRST ROIs. **Right**: Using ROIs resulting from the proposed method. Note that only 8 subjects could be used for the analysis of the default FIRST method.