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Original contribution

An improved FSL-FIRST pipeline for subcortical gray matter segmentation to study abnormal brain anatomy using quantitative susceptibility mapping (QSM)

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ABSTRACT

Accurate and robust segmentation of subcortical gray matter (SGM) nuclei is required in many neuroimaging applications. FMRIB's Integrated Registration and Segmentation Tool (FIRST) is one of the most popular software tools for automated subcortical segmentation based on T_1-weighted (T1w) images. In this work, we demonstrate that FIRST tends to produce inaccurate SGM segmentation results in the case of abnormal brain anatomy, such as present in atrophied brains, due to a poor spatial match of the subcortical structures with the training data in the MNI space as well as due to insufficient contrast of SGM structures on T1w images. Consequently, such deviations from the average brain anatomy may introduce analysis bias in clinical studies, which may not always be obvious and potentially remain unidentified. To improve the segmentation of subcortical nuclei, we propose to use FIRST in combination with a special Hybrid image Contrast (HC) and Non-Linear (nl) registration module (HC-nlFIRST), where the hybrid image contrast is derived from T1w images and magnetic susceptibility maps to create subcortical contrast that is similar to that in the Montreal Neurological Institute (MNI) template. In our approach, a nonlinear registration replaces FIRST's default linear registration, yielding a more accurate alignment of the input data to the MNI template. We evaluated our method on 82 subjects with particularly abnormal brain anatomy, selected from a database of >2000 clinical cases. Qualitative and quantitative analyses revealed that HC-nlFIRST provides improved segmentation compared to the default FIRST method.

1. Introduction

Robust and accurate brain image segmentation is an essential prerequisite for a sensitive and unbiased identification of differences in MR image intensity or volume of brain structures between normal and pathologically affected brains. Clinical imaging studies encompassing large cohorts of patients and controls commonly apply automatic image segmentation tools. To date, several sophisticated software packages have been developed for segmenting subcortical gray matter (SGM) [1–4], most of them relying on high-resolution T_1-weighted (T1w) images. Among them, FMRIB's Integrated Registration and Segmentation Tool (FIRST) [3] of the FMRIB Software Library (FSL) is one of the most popular packages. FIRST has been applied in multiple brain imaging studies to investigate volume and shape changes of

Abbreviations: QSM, quantitative susceptibility mapping; SGM, subcortical gray matter; FIRST, FMRIB's Integrated Registration and Segmentation Tool; T1w, T_1-weighted; T1n, bias-field corrected and intensity normalized T_1-weighted images; MNI, Montreal Neurological Institute; FSL, FMRIB Software Library; HC, hybrid contrast; nl, non-linear; MS, multiple sclerosis; V-SHARP, sophisticated harmonic artefact reduction for phase data with varied radii; HEIDI, homogeneity enabled incremental dipole inversion; FAST, FMRIB's Automated Segmentation Tool; FLIRT, FMRIB's Linear Image Registration Tool; ANTs, Advanced Normalization Tools; SSIM, structural similarity; eRWT, extended Regression Without Truth; CC, cross correlation.

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subcortical brain structures that may be associated with normal aging [5,6] or neurodegenerative diseases, like Alzheimer's disease [7,8], schizophrenia [9], multiple sclerosis [10], or epilepsy [11]. It has also been shown quite recently that FIRST performs similarly well regarding hippocampal segmentation to predict the progress in Alzheimer's Disease dementia when compared to other volumetric methods (e.g., Statistical Parametric Mapping) [12]. The scan-rescan reliability of SGM segmentation with FIRST on the same scanning platform [13] as well as between different scanning platforms [14] has been confirmed, which warrants the applicability of FIRST in large-scale longitudinal and multisite studies.

Brain atrophy is a hallmark of many neurological diseases, including stroke, traumatic brain injury or Alzheimer's disease [15–17], and has long been one of the primary targets of neuroimaging research. Specifically, it is correlated with disability in multiple sclerosis (MS) [18]. Consequently, if suboptimal and less accurate segmentation results occur with brain anatomies that show deviations from the anatomy of the training datasets, an analysis bias may consequently follow in clinical studies, which commonly compare patients with abnormal brains with matched controls with normal brains. This bias may not always be obvious and may even remain unidentified, especially in large-cohort studies. In this study, we therefore aim to improve the accuracy of FIRST-based segmentation of subjects with abnormal brain anatomy due to severe atrophy (see Fig. 1).

FIRST is a model-based subcortical brain segmentation tool, which models each subcortical structure as a surface mesh within a Bayesian framework, using shape and signal intensity information of manually segmented subcortical structures in 336 T1w datasets (including, but not limited to, normal brains and cases of schizophrenia and Alzheimer's diseases) as a prior [3]. The individual T1w images are linearly (affine) registered to the Montreal Neurological Institute (MNI) space using a two-stage registration with weighting of subcortical structures during the second stage. Subsequently, applying the inverse transformation brings the Bayesian model into the native space of the individual T1w images. Small inaccuracies resulting from the affine registration step are usually overcome by FIRST by applying sophisticated fine-tuning of the surface mesh. Because it may be difficult or even impossible to straighten out fully severe registration inaccuracies by the surface mesh optimization, there is consequently an intrinsic demand to transform as accurately as possible the individual subject data into the MNI space. While it is usually possible to transform brain images of healthy adults relatively accurately to the MNI space, affine registration of brain images of patients or individuals with substantial brain atrophy may produce residual misalignment in various brain structures (see Fig. 2). One reason for this is that the MNI template originates from a healthy adult population (age 18.5–43.5 years) [19,20] and that affine registration is unable to deform and resolve local shape dissimilarities. Recently, Amann et al. [21] reported that linear registration to MNI space within the FIRST pipeline is prone to fail with T1w images of patients showing global brain atrophy, and suggested to replace the MNI template by a new template that includes advanced atrophy. However, while such a modification might result in a better matching of abnormal cases, it does not account for the need to affect FIRST's internal data modelling of the residual shape variance. The use of sub-group specific templates may also introduce further types of bias in the analysis of different subject groups. In addition, region-specific and/or pathology-related brain atrophy may occur [22–24], which cannot be covered by only a single template. Therefore, a more general approach is required to account for individual shape dissimilarities in cases of diseased brains.

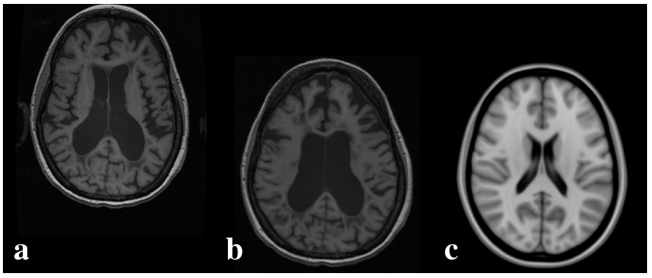

Fig. 2. Linear registration to the MNI space of a T1w image of one subject with severe atrophy. (a) shows an axial view of the original T1w image, (b) the linearly registered T1w image, and (c) the corresponding MNI template. While the position misalignment between the original T1w image (a) and the MNI template (c) can be resolved by applying a translation during linear registration, the mismatch of the ventricles and the caudate nuclei, however, remain between the registered image (b) and the MNI template (c).

Another important issue regarding FIRST-based SGM segmentation is the observation that, depending on T1w sequence parameters of the clinical imaging protocols, SGM nuclei may exhibit deviating or even poor contrast on T1w images compared to that in FIRST's training datasets, which may further affect the segmentation accuracy [25]. While the MNI template shows detailed delineation of SGM structures with excellent contrast, a similar contrast is desirable to have available with FIRST to improve inferior segmentation results in cases of insufficient contrast on T1w images. Against this background, we aim to enhance the contrast of T1w images to render their appearance more similar to the MNI template by combining T1w images with a second MRI dataset that displays SGM nuclei with distinct contrast.

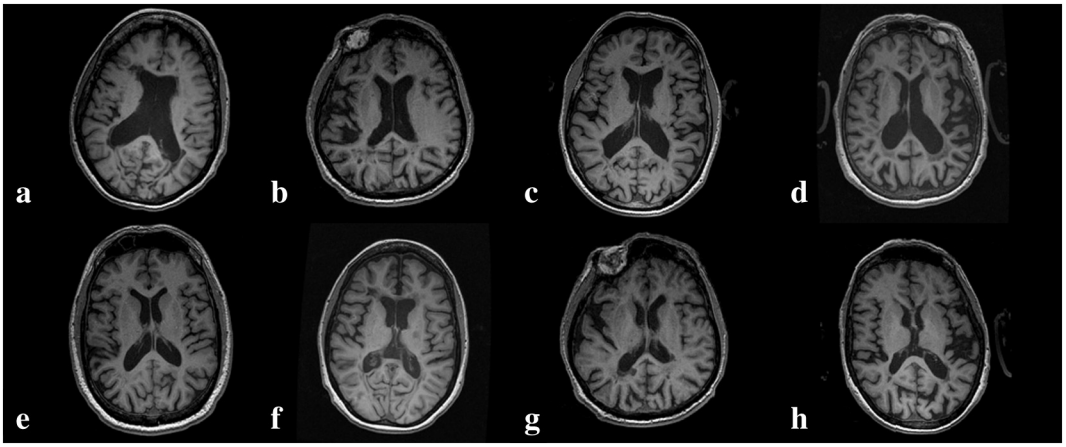

Fig. 1. Representative examples of T1w images of eight subjects who were included in the study showing particularly abnormal brain anatomy (atrophy).