



Universiteit
Leiden
The Netherlands

Quantitative analysis of human brain MR images at ultrahigh field strength

Doan, N.T.

Citation

Doan, N. T. (2014, June 17). *Quantitative analysis of human brain MR images at ultrahigh field strength*. Retrieved from <https://hdl.handle.net/1887/26921>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/26921>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/26921> holds various files of this Leiden University dissertation

Author: Doan, Nhat Trung

Title: Quantitative analysis of human brain MR images at ultrahigh field strength

Issue Date: 2014-06-17

7

Summary and conclusion

7.1 Summary and conclusion

Alzheimer's (AD) and Huntington's (HD) diseases are among the most devastating and costly neurodegenerative diseases. Finding biomarkers for early detection of AD and for disease monitoring as well as therapeutic agent assessment of HD has been a long-standing research goal for neuro-scientists. Post-mortem studies have demonstrated the association between AD and HD with abnormal iron accumulation in the brain structures such as the basal ganglia and the cerebral cortex. T_2^* -weighted imaging provides a non-invasive means to study susceptibility changes of substances such as myelin and iron in the brain. Particularly, phase images show an increased sensitivity to magnetic susceptibility differences with increased field strength. The main goal of the thesis was to develop methods for quantitative analysis of human brain T_2^* -weighted images at ultrahigh field strength. Additionally, we also aimed to investigate textural features for classification of AD in a deformation-based context.

Chapter 1 of the thesis provided an overview of AD and HD as well as T_2^* -weighted imaging at ultrahigh field strength. We highlighted the increased interest in using ultrahigh field T_2^* -weighted images for susceptibility studies of the diseases and the need to develop quantitative analysis techniques making use of these images. A brief review of texture analysis and its application in neuro-MR image analysis was presented. Finally, this chapter summarized the goals and contributions of the thesis.

In **chapter 2**, we proposed a quantitative analysis framework composed of 7T T_2^* -weighted imaging and a second order texture analysis approach. Textural features were computed from both the magnitude and phase images and subsequently used for group-wise comparison. We applied the proposed approach to study textural differences in subcortical structures between pre-manifest HD, manifest HD and control subjects. While the magnitude-based features showed differences in the pallidum in manifest HD, the phase-based features showed differences in the caudate nucleus and in both the caudate nucleus and putamen in premanifest HD and manifest HD, respectively. Our study reported the first evidence of textural heterogeneity of subcortical structures in HD. The regional specific textural differences found are in line with existing findings on structural deficits in both premanifest and manifest HD.

While chapter 2 focused on subcortical structures, chapters 3, 4 and 5 dealt with

the cerebral cortex. In **chapter 3**, we presented a new method for segmentation of the cerebral cortex from 7T T_2^* -weighted images. We first discussed the need to develop a new method that allows to perform the segmentation directly on T_2^* -weighted images. Manual segmentation is not feasible as it is not only time consuming but also subjected to inter-subject variability. Segmentation based on T_1 -weighted images suffers from the decreased GM/WM contrast due to aging effect. The proposed method was based on K -means clustering of the magnitude and phase images. It combined magnitude and phase information in a two-step framework. In the first step, the outer contour of the cortex was segmented using the magnitude information. Subsequently, an initial inner contour was estimated using the combined magnitude and phase information, thereby obtaining the initial segmentation of the cortex. In the second step, this initial segmentation was further refined using a mathematical tool called transformation with reconstruction criteria to obtain the final segmentation. We evaluated our method using the manual segmentations and the T_1 -based segmentations obtained using FreeSurfer and FSL, two state-of-the-art methods. Our method showed good agreement with the manual segmentation and a superior performance compared to the T_1 -based approaches.

Chapter 4 presented a method for local group-wise analysis of the cerebral cortex. The cortex was segmented using the method presented in chapter 3 and parcellated using an atlas with predefined cortical areas. Subsequently, local GM/WM contrast and local cortical profile were computed automatically at each parcellated cortical ROI. Group-wise comparison in terms of local GM/WM contrast was performed using a Mann-Whitney U-test. To compare local cortical profiles, we used two permutation tests, one using the entire profile and one performed at each node on the profile. We applied the method to compare a group of young subjects and a group of elderly healthy subjects. Using local phase and magnitude GM/WM contrast, differences were shown in 14 and 15 of 17 studied regions, respectively. Localized differences in phase and magnitude profiles were revealed in 16 and 17 regions, respectively. The local comparison at each cortical depth highlighted differences in the centre and boundaries of the cortex. The differences found were in line with existing literature and could be explained by known changes in myelin and iron content as an effect of aging. The results showed that the method can be a useful tool in studying normal aging and might also be useful in studies of neurodegenerative diseases.

In **chapter 5**, we explored regional differences between early onset AD (EOAD) patients and late onset AD (LOAD) patients using MR phase images. We manually measured peak phase shift from four different lobes in the brain and applied the method presented in chapter 4 to compute GM/WM phase contrast and cortical phase profile at several local cortical regions. Subsequently, we applied a linear regression model adjusted for gender and the disease severity, quantified by MMSE score, to assess group differences in terms of lobar phase shift and local GM/WM contrast. The differences in cortical profiles were evaluated using two permutation tests as described in chapter 4. The results showed that subjects with EOAD had a larger cortical phase contrast and a more severely affected cortical layer pattern compared to LOAD subjects, especially in the middle frontal gyrus, postcentral gyrus, superior parietal gyrus, and precuneus. These results indicate that patients with EOAD have an increased iron accumulation possibly related to an increased amyloid deposition in specific cortical regions compared to LOAD patients.

Finally, in **chapter 6**, we investigated the use of deformation-based textural features in

classification of AD and compared the added value of registration to a single template and pairwise registration in such a classification framework. In our approach, T_1 -weighted images of 92 subjects were non-rigidly registered to a template. Textural features were derived from the Jacobian determinant map of the resulting deformation field of the entire brain using the Gray Level Co-occurrence Matrix (GLCM) approach. PCA was applied on the large set of computed features for feature reduction. The retained features were used as an input of a linear support vector machine for classification. Classification performance was evaluated using a bootstrapping procedure. We compared the method with two dissimilarity-based approaches, one based on pairwise registration and the other based on registration to a template. We showed in the context of this study that pairwise registration did not bring added value compared to registration to a single template and textural features were more informative than dissimilarity-based features. Our study demonstrates the potential of texture analysis on the Jacobian determinant map over the entire brain for diagnosis of AD subjects.

Considering the work presented in **chapters 2-6**, we believe that we have achieved the goals formulated in Section 1.5. We set up a framework for texture analysis of subcortical structures using 7T T_2^* -weighted images (**chapter 2**). Application of the framework was demonstrated in HD. In terms of cortical analysis, a new algorithm for segmentation of the cortex from 7T T_2^* -weighted images was proposed and extensively validated (**chapter 3**). This development enabled further steps in quantification of changes in the cortex. Subsequently, we developed a highly automated method for detecting regional changes in GM/WM contrast and cortical profile at multiple cortical ROIs (**chapter 4**). In addition to an analysis of aging effect using data of young and old healthy subjects (**chapter 4**), this method was also applied in an in vivo study of AD patients (**chapter 5**). Besides, the use of textural features derived from the deformation field was addressed (**chapter 6**). Even though the classification performance was moderate, the results demonstrated the potential of using deformation-based textural features in classification of AD.

7.2 Future work

Phase unwrapping is an important preprocessing step in phase-based analysis. Throughout this thesis, we used a high-pass filtering technique [25] to perform this operation. Even though this technique has been widely used in the literature, one disadvantage is that, depending on the kernel size used, it could lead to information loss or artifacts remaining in areas with very steep transitions [191]. Non-filtering techniques such as SHARP [192] and PRELUDE [193] could be considered as alternatives.

Image phase has some limitations. It is affected by the structure geometry and tissue orientation with respect to the main magnetic field. Furthermore, it has been shown that the phase image has a non-local relation with the underlying tissue susceptibility. Much research is focusing on developing quantitative susceptibility mapping techniques [143, 144] that can provide an estimation of tissue susceptibility map based on phase images. The texture analysis and group-wise cortical analysis frameworks could be easily adapted to derive cortical features from a susceptibility map. It should be mentioned that the cortex segmentation step would still require the combined magnitude and phase information.

In chapter 4, we investigated two cortical features, local cortical GM/WM contrast and cortical profile, on magnitude and phase images. Other cortical characteristics, for instance, local inhomogeneity can be visually observed on the phase images. Further

work should focus on deriving cortical textural features. For that purpose, the GLCM approach deployed in chapter 2 for subcortical structures could be extended to analysis of the cortex. While computing GLCM, the search direction should be adapted at each voxel being considered using the norm of the outer cortical surface at that voxel as the reference direction.

The performance of AD classification presented in chapter 6 was moderate. Textural features were derived solely from the entire brain deformation field, which was strongly dependent on the registration settings. In this study, we used B-Spline registration in a multi-resolution non-rigid registration framework. At the finest resolution, a relatively large grid spacing of 15mm was empirically chosen to avoid physiology-meaningless "foldings" in the deformation field. A disadvantage is that the deformation may not be sensitive to small local changes such as changes in the accumbens nucleus [194] or in thickness of the cerebral cortex [195]. Further research could examine the use of smaller grid spacings in combination with a bending penalty term. Additionally, multi-resolution texture analysis techniques such as Wavelet-based approaches [39] could be investigated.

In this thesis, application of the methods developed for 7T T_2^* -weighted image analysis has been demonstrated in normal aging, Alzheimer's disease and Huntington's disease. Nevertheless, they can also be applied in the context of other neurological diseases such as Parkinson's disease and multiple sclerosis where clinical studies have reported alterations in iron content of the brain structures [77, 196].

Due to the much higher cost of a 7T human MRI system compared to a 3T system (7M \$ vs. 3M \$) and further technical development needed for 7T, it is not likely that 7T MRI will replace 3T MRI in the near future. Therefore, it would be interesting to check if the developed methods can be translated to 3T. However, it should be noted that susceptibility-based studies performed at 7T would benefit from an increased sensitivity with respect to tissue magnetic susceptibility compared to 3T.

Iron has been shown to play an important role in normal aging and neurological disease processes. In my opinion, T_2^* -weighted imaging at ultrahigh field holds great promise to be a useful tool for in vivo studies of brain iron. Constant effort has been dedicated to designing sequences and hardware to improve the quality of images acquired at ultrahigh field. Images with higher resolution and sensitivity to tissue susceptibility are possible to obtain. Image processing techniques such as those presented in this thesis would be good candidates for extracting useful information from ultrahigh field T_2^* -weighted magnitude and phase images.