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Registration of in-vivo to ex-vivo MRI of surgically resected specimens: A pipeline for histology to in-vivo registration

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HIGHLIGHTS

- We present a protocol for registration of in-vivo to ex-vivo brain specimens.
- This protocol completes a registration pipeline for histology to in-vivo MRI.
- A TRE of 1.35 ± 0.11 mm (neocortex) and 1.41 ± 0.33 mm (hippocampus) was found.
- Deformable registration significantly improved the registration accuracy.
- This pipeline allows for the assessment of pathological correlates in MRI.

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ABSTRACT

Background: Advances in MRI have the potential to improve surgical treatment of epilepsy through improved identification and delineation of lesions. However, validation is currently needed to investigate histopathological correlates of these new imaging techniques. The purpose of this work is to develop and evaluate a protocol for deformable image registration of in-vivo to ex-vivo resected brain specimen MRI. This protocol, in conjunction with our previous work on ex-vivo to histology registration, completes a registration pipeline for histology to in-vivo MRI, enabling voxel-based validation of novel and existing MRI techniques with histopathology.
New method: A combination of image-based and landmark-based 3D registration was used to register in-vivo MRI and the ex-vivo MRI from patients ($N = 10$) undergoing epilepsy surgery. Target registration error (TRE) was used to assess accuracy and the added benefit of deformable registration.
Results: A mean TRE of 1.35 ± 0.11 and 1.41 ± 0.33 mm was found for neocortical and hippocampal specimens respectively. Statistical analysis confirmed that the deformable registration significantly improved the registration accuracy for both specimens.
Comparison with existing methods: Image registration of surgically resected brain specimens is a unique application which presents numerous technical challenges and that have not been fully addressed in previous literature. Our computed TRE are comparable to previous attempts tackling similar applications, as registering in-vivo MRI to whole brain or serial histology.
Conclusion: The presented registration pipeline finds dense and accurate spatial correspondence between in-vivo MRI and histology and allows for the spatially local and quantitative assessment of pathological correlates in MRI.

1. Introduction

Approximately 30% of all patients with epilepsy are considered medically intractable, that is about one third of patients do not achieve remission with antiepileptic drugs (Engel, 1998). Surgical excision of the affected brain region is an effective treatment

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for drug-resistant focal epilepsy (Engel et al., 1992), with a recent long-term clinical study of surgical outcomes reporting that fewer than 60% of patients remained seizure-free at 10 years follow up (de Tisi et al., 2011). Such data have motivated the need for better pre-operative imaging and image analysis techniques to locate the epileptogenic foci and disease-related pathological tissue more accurately and provide better surgical planning. Current clinical magnetic resonance imaging (MRI) protocols lack sensitivity, as more than 30% of patients have no evidence of brain lesions (Sylaja et al., 2004). Quantitative techniques such as diffusion tensor imaging (DTI), relaxometry mapping, voxel-based morphometry, and cortical thickness analysis have demonstrated increased sensitivity in lesion detection over routine or clinical MRI protocols (Bernasconi et al., 2000, 2004; Bernhardt et al., 2009). These techniques have the potential to better delineate the epileptogenic zone and thus improve surgical outcomes, however, validation is currently needed to investigate and describe histopathological correlates of these imaging techniques (Eriksson et al., 2007; Howe et al., 2010). In order to carry out this validation effectively, accurate registration must be performed to obtain a dense spatial correspondence between in-vivo MR images and histology images of surgical specimens.

MRI to histology registration is far from trivial due to the significant deformations undergone by the brain tissue during surgery, handling, and histological processing. These deformations can be split into two main categories, those occurring during surgical resection and those during histological processing (Dauguet et al., 2007). Those due to surgical resection are three dimensional mechanical deformations that take place once brain tissue is resected, due to its tendency to deform when separated from neighbouring tissue. The histological processing deformations are three dimensional, occurring during sectioning or due to non uniform shrinkage induced by formalin fixation, as well as two dimensional (within-slice) distortions due to stretching of microtome cut sections on a water bath, spreading histology slices over glass slides and staining. The deformations induced during histological processing can be isolated from those from surgery and handling by employing an intermediary MRI image of the specimen or using blockface images for histological reconstruction, splitting the in-vivo MRI to histology registration procedure into two distinct problems (in-vivo to reference and reference to histology). As described in our previous work registering ex-vivo MRI to sparsely sectioned hippocampal and neocortical temporal lobe specimens, the intermediate ex-vivo MRI or blockface stack can function as an anatomical reference with which the 2D histological slices can be corrected against (Goubran et al., 2013). In this work, however, we focus on the first problem of registering the in-vivo MRI to the intermediate ex-vivo MRI, and completing a pipeline for histology to in-vivo MRI registration in temporal lobe epilepsy.

There have been many attempts in the literature to register in-vivo MR images of many organs, such as the prostate (Ward et al., 2010; Chappelow et al., 2011), to histology slices. Extrapolating these registration techniques to the brain may not be practical since the brain has very different biomechanical properties than other organs and is prone to deformation. Moreover, algorithms optimized for registering other resected organs generally do not deal with part-to-whole registration, and thus may not be applicable in our problem. In the past two decades, there have also been many studies specifically dealing with in-vivo brain MRI to post-mortem histology. The majority of these studies focused on primates (Dauguet et al., 2007; Malandain et al., 2004; Breen et al., 2005; Ceritoglu et al., 2010; Choe et al., 2011) or rodents (Jacobs et al., 1999; Humm et al., 2003; Meyer et al., 2006; Lebenberg et al., 2010; Yang et al., 2012; Liu et al., 2012). The few studies that registered human brain MRIto histology were performed on whole-brain (Schormann et al., 1995; Kim et al., 2000; Singh et al., 2008), or single hemisphere (Yelnik et al., 2007; Osechinskiy and Kruggel, 2011) post-mortem serially sectioned data (Amunts et al., 2013) created a 3D model of single subject's brain using post-mortem histological sections reconstructed at 20 μm isotropic resolution and registered it to a T1 average atlas created from 24 subjects. Eriksson et al. (2005) reported registering histology of neocortical specimens from anterior temporal lobectomies to in-vivo MRI; however, their approach only involved visually selecting the closest coronal MRI slice for each histology slide, and did not attempt to find a dense correspondence between each histology slide and its corresponding MRI slice.

This study focuses on finding correspondences between in-vivo and ex-vivo MRI, which enables the validation of in-vivo imaging findings using higher-resolution ex-vivo scans. It also bridges information from histology to ex-vivo data and finally to the clinically relevant pre-operative images when combining our previous work with the current study. Image registration of a deformed cut specimen to the original brain, that is part-to-whole registration, is challenging because similarities between the images have been constrained to a meaningful sub-region of the in-vivo image that is variable from specimen to the other (due to different resection strategies and substantially variable specimen shapes and volumes). The presented registration approach for this problem employs an automated initialization as well as a landmark-based rigid registration, followed by a landmark deformable registration for hippocampal specimens and an image-based non-rigid warping for neocortical specimens. Using anatomical landmarks is a reliable technique for registration that exploits the operator's anatomical expertise and enforces registration constraints based on the placed landmarks.

2. Methods

2.1. Recruitment, surgery and specimen acquisition

Temporal lobe epilepsy patients who were candidates for anterior temporal lobectomy (ATL) surgery were recruited for this study. Patients had preoperative investigations including neuropsychological testing and 1.5 T clinical MRI scans which included T1w, T2w, FLAIR, and diffusion-weighted sequences. Patients were monitored with scalp-based electroencephalogram (EEG) video telemetry for seizure characterization, with three patients requiring subdural electrodes placement. In addition to the 1.5 T clinical MRI scans performed at the hospital, patients underwent a series of scans on 3T and 7T MRI research scanners, described in the in-vivo MRI subsection. Our study cohort included 10 temporal lobe patients who underwent epilepsy surgery and the resection of two specimens, temporal lobe neocortex and hippocampus, as part of an ongoing project at the Robarts Research Institute. Two hippocampal specimens were not obtained en-bloc due to the use of the cavitron ultrasonic surgical aspirator (CUSA) device during surgery, and were thus excluded from this study. This project was approved by the office of research and ethics of Western University, and informed consent was obtained from all patients prior to their recruitment in the study. Table 1 summarizes the age, gender, onset age, seizure origin as well as clinical MRI and pathology findings for our patient cohort.

2.2. Patient in-vivo MR Imaging and maps generation

All patients underwent pre-operative imaging on a 3 T Discovery MR750 scanner (General Electric, Milwaukee, WI, U.S.A.) with a 32 channel head coil and consisted of relaxation mapping, diffusion-tensor imaging and resting-state functional imaging. For T1 mapping the 'DESPOT1-HIFI' approach (Deoni, 2007)