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MRI/SPECT-based diagnosis and CT-guided high-intensity focused-ultrasound treatment system in MPTP mouse model of Parkinson's disease

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ABSTRACT

Single-photon emission computed tomography (SPECT) of dopamine transporters with ^{99m}Tc-TRODAT-1 has recently been proposed to offer valuable information for the diagnosis of Parkinson's disease (PD). Furthermore, High-intensity focused ultrasound (HIFU) is a newly developed technique in which the energy of ultrasound wave is directed to a focused spot for the purpose treatment of PD. This study presents a diagnosis and image-guided system using HIFU to treat the mouse with PD under a designed stereotactic frame. The system comprises two key components: an automatic atlas-based SPECT/MRI image registration module for diagnosis and a stereotactic CT-guided module for HIFU treatment. The SPECT/MR image registration here is important in the non-invasive examination of the dopamine concentration *in vivo*. From the experimental results, the image registration module proves to have comparable performance to that derived from manual drawing by experts. In addition, the stereotactic CT-guided module achieved a positioning accuracy to within 2 mm on the average, which is acceptable for the purpose of HIFU treatment.

1. Introduction

Parkinson's disease (PD) is a progressively neuro-degenerative disorder characterized by symptoms, including akinesia, rigidity and tremors. According to current understanding, PD pathology results primarily from the reduction of dopamine-secreting cells in the pars compacta of the substantia nigra. Such reduction can also be found in nucleus basalis, hypothalamus, cerebral cortex and other cranial nerve system.

The state of the art for PD diagnosis relies on neuroimaging techniques comprising functional image modalities such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), and anatomical image modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). In the clinical application of PD, functional imaging techniques provide useful information for detecting *in vivo* metabolic and neuro-chemical changes characterizing of PD pathology. Recent researches have shown that ^{99m}Tc-TRODAT-1 is useful in the diagnosis of PD [1] because TRODAT-1 can bind to the dopamine transporter sites at pre-synaptic neuron membrane and can easily be labeled with ^{99m}Tc. For example, observe the T2-Weighted MRI as shown in Fig. 1(a), it is difficult to differentiate the healthy mouse brain from that of the mouse with Parkinson's, but with use of the ^{99m}Tc contrast medium the SPECT can very clearly distinguish the pathological Parkinson's mouse from the healthy mouse, as seen in Fig. 1(b) and (c) (indicated by cross mark), respectively. Thus the ^{99m}Tc-TRODAT-1 has been clinically proven to improve diagnosis of the condition of dopamine neuron. Hence, in a clinical diagnosis of PD, the fusion image of MRI and SPECT is adopted to help physicians compute a quantitative index of the specific-to-non-specific binding ratio (BR) of ^{99m}Tc-TRODAT-1 to dopamine transporters in the regions of interest (ROIs). This index enables the accurate evaluation of complex pre-, post- and intra-synaptic dopaminergic phenomena in a living brain to clarify better the pathophysiology of PD and related syndromes. Accordingly, a suitable or even automatic algorithm for MRI/SPECT registration is useful in aiding clinical diagnoses.

A survey of the literature revealed that multi-modality small animal image registration relied primarily on the techniques of automated image registration (AIR) [2,3] as well as maximization of mutual information (MI) [4,5]. Nevertheless, these methods were unstable if non-brain structures were not removed before performing registration. To overcome this drawback, we have developed an image registration algorithm which takes into consideration both the distribution of image intensity and the contour information of ROIs [6].

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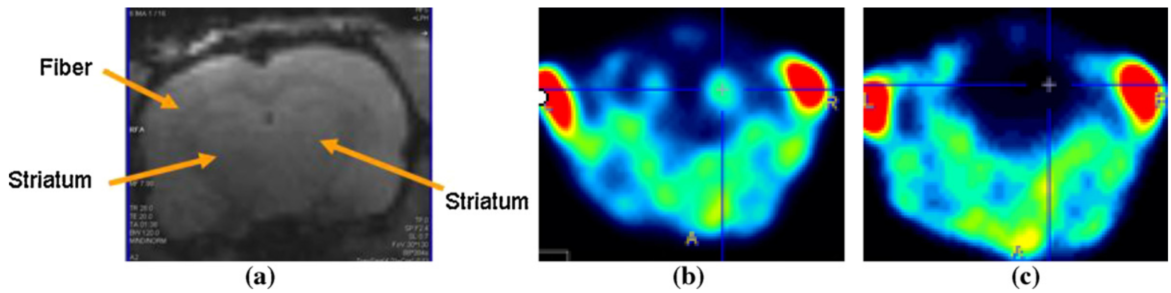

Fig. 1. Example of T2-weighted MRI and 99mTc-TRODAT-1 SPECT, (a) MRI Image, (b) SPECT image from a healthy mouse, (c) SPECT image from a Parkinson's mouse.

First of all, one set of MRI taken from a particular mouse, with pre-selected ROIs reflecting the striatum structure, were used as templates. These ROIs were manually drawn by a clinical expert. Then these templates were utilized to automatically segment the striatum structure for other MR images taken from other mice. Next, the SPECT and MRI were co-registered to determine the precise distribution and location of the striatum. Finally the mentioned BR, calculated according to Eq. (1), was employed to evaluate the changes of a Parkinson's mouse in brain organization and function.

$$BR = \frac{R_S - R_{OCC}}{R_{OCC}} \quad (1)$$

where R_S and R_{OCC} represents the mean counts per voxel within the striatum structure and the occipital cortex (background), respectively.

Surgical treatment of PD has evolved into a very advanced method during the past few decades. Common surgical treatment techniques include pallidotomy, thalamotomy and deep-brain-stimulation [7–9]. Such treatment is especially useful for PD patients whose symptoms are too advanced to be treated by drug alone. However, these surgical treatment techniques are invasive in nature and therefore have a higher risk of complication.

High-intensity focused ultrasound (HIFU) is a newly developed technique in which the energy of ultrasound wave is directed to a focused spot for the purpose of ablation of unwanted tissue by heat. It does not have the drawback of invasiveness incurred by the above-mentioned surgery treatment techniques. Consequently, HIFU has the potential of becoming a minimally invasive alternative to traditional surgery methods if highly accurate positioning at any arbitrary region of the deep brain can be achieved. Recent studies also have demonstrated the feasibility of transcranial HIFU therapy [10]. HIFU is expected to provide advanced treatment for not only brain tumor but also neurologic disorders. However, before practically applying the HIFU on a human body, plenty of animal trails need to be performed to evaluate and analyze its clinical impacts. Therefore, an image-guided stereotactic module for HIFU treatment on mouse with PD is designed in this study.

To sum up, a computer-aided system which comprises a MRI/SPECT registration module and an image-guided stereotactic module is presented. The former measures the index of BR for clinical evaluation, while the latter provides accurate spatial localization for HIFU targeting on PD mouse. The contributions are listed as follows:

1. Appling the atlas-based MRI/SPECT registration proposed in [7] to PD/normal mice instead of human beings.
2. Designing a new stereotactic frame to hold a mouse for a CT-based image-guided system.
3. Integrating a HIFO device into the image-guided system for treatment of PD mouse.
4. Developing a computer-aided system by integrating the MRI/SPECT registration module and the image-guided system with a SPECT/CT scanner for PD mouse study.

The organization of this paper is summarized as follows. In Section 2, we describe the proposed system and the details of its components. Sections 3 and 4 show experimental results and discussions respectively. Conclusions are revealed in the final section.

2. Proposed system

The proposed system comprises two major components: (1) atlas-based MRI/SPECT registration for the diagnosis of mouse with PD, and (2) 3D stereotactic image-guided system for HIFU treatment. When a PD/normal mouse is fixed in a stereotactic frame and scanned by a SPECT/CT scanner, the system operates with the two modules by using the obtained CT and SPECT images, a pre-obtained MRI of the same subject, and a labeled MRI template. Since the activity of the dopamine-secreting cells in the pars compacta of the substantia nigra can be monitored by means of SPECT images utilizing ^{99m}Tc-TRODAT-1 as the radiotracer [1]. Unfortunately, the SPECT images are lack of anatomical information to distinguish which organ is responsible for the abnormally low activity of dopamine secreting. Therefore, MR imaging of the same subject that provides the needed anatomical reference through multi-modality image co-registration is needed. In addition, by registering the labeled MRI template to the pre-obtained MRI of the subject, the contours of these meaningful tissues can be overlapped on the pre-obtained MRI from the MRI template. In other words, the atlas-based MRI/SPECT registration modules deals with the registration problems among SPECT, pre-obtained MRI, and labeled MRI template and automatically highlights the ROIs for diagnosis such as BR evaluation and treatment planning.

Once the region of abnormity is located, its coordinates need to be transformed so that both the region of abnormity to be treated and the treatment equipment can be referenced under a common coordinate system. Since the mouse is fixed within a stereotactic frame, the transform is computed by registering the landmarks of the frame shown on the CT date to their locations in the physical space. Since the CT and SPECT share the same imaging coordinate system by using a SPECT/CT scanner, the purpose of the 3-D image-guided system is the computation of such transformation which characterizes the spatial relationship between the coordinate system on which SPECT images are based and the coordinate system on which the treatment equipment is based. Therefore, the ROIs in SPECT are thus reachable by using the HIFU for further treatment.

2.1. Atlas-based MRI/SPECT registration

Quantitative characterization of PD requires precise measurement of radioactivity concentrations within the striatum which in turn needs to be delineated precisely first. But the SPECT image