Validation of T1-weighted inter-subject MRI registration technique for atlas warping in identifying the subthalamic nucleus, red nucleus, and substantia nigra

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Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for Parkinson's disease (PD). Since the STN has a small size, and is divided into three functional regions (motor, associative and limbic), it is important to localize the stimulation target and its surrounding structures to avoid undesirable side-effects and gain the best therapeutic benefits for the patients. So far, both direct and indirect methods have reported success in locating the stimulation targets [1]. Among the current MRI techniques for direct delineation of the STN on a subject, susceptibility-based methods (i.e. T2*w image and T2* map) offer better contrast [2] while the T2w FSE is still the "state of the art". In many indirect atlas-based nuclei identification methods [1], T1w-T1w image registration was often applied to estimate the atlas warping. However, the red nucleus (RN), substantia nigra (SN), and subthalamic nucleus (STN) are not well visualized on the T1w image. Although the rough location of the STN was confirmed by electro-physiological recording in several atlas-based targeting techniques [1], whether the T1w-T1w registration based atlas warping is sufficient to account for the inter-subject variability remains unknown. In this abstract, we employ the Colin27 template-to-subject registration method, which has been validated for the subthalamic nucleus DBS using electro-physiological data [3,4], to deform the labels of SN, RN, and STN, defined on the T2w image of Colin27 dataset, and compare them to the MR images (T2*w image and R2* map) from normal controls and patients acquired on a 3T scanner.

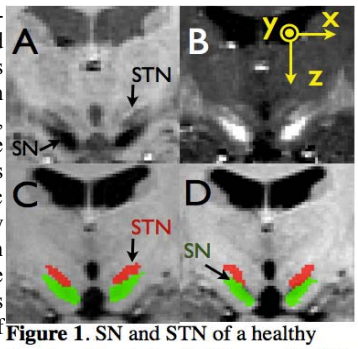

Figure 1. SN and STN of a healthy female subject. A = T2* image; B=R2* map; C = manual segmentation overlaid on T1w image; D = registered Colin27 labels overlaid on T1w image

Methods: After providing informed consent, 2 healthy subjects (male, 24yr & female, 41yr) and 4 PD patients (1 female, 3 male, age = 56±6yr) volunteered for the study. Each subject was scanned on a 3T MRI scanner (Siemens Trio, Erlangen, Germany) with a 10 echo 3D FLASH MRI protocol: TE={1.6, 4.1, 6.6, 9.1, 13.0, 16.0, 18.5, 21.0, 23.5, 26.0}ms, TR=30ms, flip-angle=23°, BW=±450 Hz/pix, matrix=256x256, 176 sagittal slices, resolution= 0.95x0.95x0.95mm^3, 6/8 partial Fourier in the phase and slice encoding directions, and GRAPPA=2. From the MRI data acquired, three image contrasts (T1w image, T2*w image, and R2* map) were generated. The T1w image was produced by averaging the magnitude images of the first four echoes. The T2*w image was generated by averaging the magnitude of the last five echoes. The R2* map was derived by fitting all magnitude data to an exponential curve. The Colin T2w image was produced by de-noising [5] the average of 12 T2w images of the same subject [6], after processing each of the 12 images with: 1) registration to the Colin27 T1w image; 2) non-uniformity correction [7]; and 3) intensity normalization [8]. The final average T2w image was resampled on the same voxel grid as the Colin27 T1w image. The labels of the STN, SN, and RN were manually painted in 3D using ITK-SNAP (www.itkSNAP.org) on the Colin T2w image and on each subject using a consensus of their T2*w images and R2* maps. To verify the T1w-T1w template-to-subject registration for the nuclei segmentation, the Colin T2w-defined labels were registered to each subject by applying the global affine and local non-rigid deformation as described in [4], and compared to the manual segmentations of the susceptibility-based images using four metrics for each structure: 1) an overlap metric **kappa=2*a/(b+c)**, where **a** is the mutual volume of two segmentations, and **b** and **c** are volumes of each segmentation; 2) the Euclidean distance (**COM_Euclid**) between the centre of mass (COM) of the deformed Colin labels and manual segmentation; 3) the x-, y-, and z-coordinate differences of the COMs (**COM{x,y,z}=COM$_{Colin}$ – COM$_{manual}$**) after transforming them into Talairach space; and 4) the size differences (**Size Diff = Size$_{Colin}$-Size$_{manual}$**). All Metrics were analyzed using one-sample or paired-sample two-sided t-tests. Figure 1 shows example image contrasts and segmentations for the healthy female subject (along with x-, y-, z-coordinates, and y-axis points to the posterior direction).

Results: The evaluation of the four metrics are presented in Table 1 all 6 subjects .

	Left RN			Right RN			Left SN			Right SN			Left STN			Right STN		
Kappa	0.70±0.06			0.72±0.08			0.54±0.04			0.57±0.09			0.55±0.07			0.53±0.07		
COM_Euclid(mm)	1.24±0.42			1.06±0.54			2.56±0.30			2.07±0.69			1.35±0.42			1.52±0.63		
COM{x,y,z}(mm)	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z	x	y	z
	0.32±0.53	0.97±0.44	0.68±0.35	-0.23±0.77	0.60±0.51	0.58±0.32	0.38±0.55	-2.44±0.54	0.72±0.37	0.11±0.36	-2.00±0.75	0.70±0.20	0.26±0.64	0.79±1.06	0.52±0.66	0.35±1.07	0.34±0.98	0.60±0.56
Size Diff (mm^3)	6.72±53.44			-2.72±64.14			-196.77±109.62			-97.03±99.51			-2.86±41.58			17.58±55.09		

Table 1. The mean value and standard deviation for the metrics.

Conclusion and Discussion: Upon visual inspection, the registration-based segmentation roughly agrees with manual segmentation, and the two overlap at the "hot-spot" for STN DBS. However, through the quantitative study, detailed geometric differences were revealed between these two sets of segmentations. From the kappa evaluation, the registered Colin T2w labels match the manual segmentation better for the RN than the SN and STN ($p<0.02$). While the kappa metric showed no significant difference between the SN and STN for the quality of registration-based segmentation, the COM Euclidean distances of the SN between the registration-based and manual segmentations were the largest. However, these distances fall in the range reported previously [1]. Compared with the manual segmentation, the registration-based segmentations were more posterior and inferior for the RN ($p<0.01$), and more anterior and inferior for the SN ($p<0.01$). Lastly, only the SN demonstrated a significant size differences between the two segmentations, and the deformed SN Colin labels were significantly smaller than what appears on the T2* image and R2* maps. In contrast to the better results of the RN, the geometries of the SN and STN were not precisely captured by the registration-based segmentation. This means that the differences of the nuclei sizes and positions between an atlas and another subject may not be completely accounted for in the T1w-T1w inter-subject non-rigid registration. In our example, this is especially true for the left SN, which is significantly smaller for Colin than the group average ($p<0.01$). In addition, for PD subjects, possible neuronal loss can further complicate the size and location differences of the nuclei. This suggests that multiple contrasts (i.e. T2*w image & R2* map) should be integrated into registration-based segmentation of hypothalamic nuclei.

Reference: 1. Brunenberg *et al*. JNS (2011) 115(5) 971-984; **2.** O'Gorman *et al.* Eur Radiol. 2011 Jan; 21(1):130-6; **3.** Chakravarty *et al*. Med Image Comput Comput Assist Interv. 2006;9(Pt 2):389-96; **4.** Chakravarty *et al*. Medical Image Analysis 12 (2008) 713–726; **5.** Coupe *et al.* Med Image Comput Comput Assist Interv. 2006;9(Pt 2):33-40; **6**.Holmes *et al.* J Comput Assist Tomogr. 1998 Mar-Apr; 22(2):324-33; **7**. Nyul *et al.* IEEE Trans Med Imaging 2000 Feb;19(2):143-50; **8.** Sled *et al.* IEEE Trans Med Imaging 1998 Jun;17(3):463-8.