Automated Segmentation of Substantia Nigra - Improved Reliability for Multiparametric MR Measurements

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Introduction: The substantia nigra (**SN**) is a small midbrain structure critical for studying the pathogenesis and pathophysiology of Parkinson's Disease (**PD**). Sensitive and reliable measurements of the SN are imperative for early detection and follow-up of PD progression. Multiparametric MR, consisting of Diffusion Tensor Imaging (**DTI**), Magnetic Transfer Ratio (**MTR**) and Quantitative Susceptibility Mapping (QSM) are advanced MR modalities that have shown considerable utility in detecting early PD changes in SN [1,2,3]. However, the widely used manual method for obtaining regions of interest (**ROI**) in SN is time consuming and introduces measurement errors due to inter- and intra-rater variability. Moreover, different shapes and sizes of manual outlines have been reported due to the lack of visible anatomical boundaries of SN. The SN is difficult to identify in structural T1-weighted MRI scans, and cannot be automatically segmented with currently available software such as Freesurfer [4, 5]. Previously, a limited number of studies have attempted to segment SN using T2 and T2*-weighted images [6, 7]. QSM is a recent method that is more sensitive to intrinsic iron content than T2 and T2*, making it ideal for identifying high iron content regions of the brain including the SN [8, 9]. We present a QSM-based automated segmentation of the SN and a comparison to results from the conventional manual method.

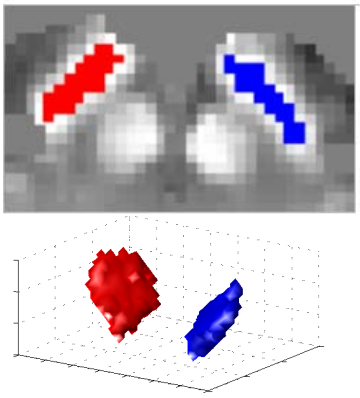

Fig.1: Automated segmentation of SN overlaid on QSM and a 3D Rendering of the segmented SN

Methods: *Demographics:* 15 subjects (Age: 66.9 +/- 6.5 yrs, 9M/6F) were included. All subjects signed an IRB approved consent form. *MR Image Acquisition:* Siemens 3T scanner (MAGNETOM Verio, Siemens, Erlangen, Germany) with a 12 channel phased array head coil was used to collect the following images: **1)** MPRAGE (TE/TR/TI/FA= 2.94ms/2300ms/900ms/9°, resolution=1x1x1mm^3; **2) DTI** 2D SE-EPI (TR=5000ms, bvalue=1000sec/mm^2, resolution = with a 2mm^3; **3) MT** 3D GRE sequence for with and without MT (TE/TR/FA= 3.92ms/30ms/5°, resolution = 1x1x1.2mm^3; **4) QSM** A T2-weighted 3D-GRE multi-echo (TE/TR/FA=3.6-45ms/55ms/15°; resolution = 0.9x0.9x1.5 mm^3). *Image Post-processing:* Dicom images were transferred to a Linux workstation where the parametric MR maps were computed. **1) FA and MD maps** were calculated for DTI images using FDT [10] **2) MTR maps** were calculated as the normalized difference between signal intensities with and without MT saturation pulse. **3) QSM** was reconstructed using a morphology-enabled dipole inversion (MEDI) algorithm [9]. *Quantitative Analysis:* Intermodal linear image registration was performed using FMRIB's Linear Image Registration Tool (FLIRT) to align the QSM image with an anatomical T1-weighted image. Next, the contents of the ventral diencephalon and brainstem masks were first generated using FreeSurfer to mask out the midbrain image containing substantia nigra. Using a hierarchy segmentation algorithm consisting of thresholding and a union-find algorithm, SN was automatically segmented using an in-house written MATLAB program. Effort was made to address partial volume artifact by excluding boundary pixels as shown in Fig. 1A. The automated ROIs were used to extract the mean values of FA, MD, MTR and QSM. Manual ROIs were placed on the SN twice by two separate experienced users for intra-rater and inter-rater comparisons. *Statistical Analysis:* Agreement between the two different methods was validated using Bland-Altman analysis to compare the multiparametric measurements of the SN obtained from manual ROI placement and our automated segmentation approach. Intraclass correlation coefficients (ICC) were calculated for the manual ROIs in order to compare reliability between the two methods.

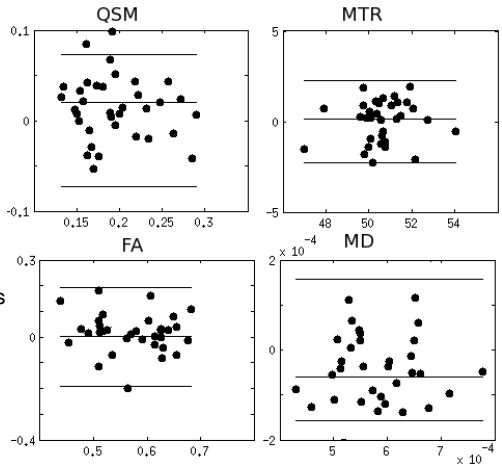

Fig 2: Bland-Altman plots demonstrating high agreement between the manual and automated method. X-axis=average between measurements, Y-axis=average difference between measurements. Horizontal bars=2SD and Mean.

Results and Discussion: Fig. 1 demonstrates the automated segmentation results of SN. As shown in Fig. 2, Bland-Altman tests indicate good agreement between automated and manual measurements of all four modalities studied (FA, MD, MTR and QSM), suggesting the automated and the conventional manual methods are interchangeable. Compared to the manual measurements, a systematic (~0.02 ppm) increase in automated QSM and reduction of (0.5 x 10^{-4} mm^2/s) MD is observed. Inter and intra-rater reliability of manual and the automated method is summarized in Table 1. For the manual method, measurement reliability for MTR and QSM were acceptable (ICC>0.7, table 1). However, DTI metrics were all below acceptable limits with a manual inter-rater reliability of only 0.41-0.54 for FA and MD. Contrastingly, our automated method with no user intervention generates objective and reliable results for FA, MD, MTR and QSM and outperformed the manual method, achieving an ICC= 1.0 both within and between operators without introducing any inter- and intra-rater bias in the measurements derived with our automated approach.

Table 1: Reliability of Substantia Nigra MR Measurements

	QSM		MTR		FA		MD	
Inter-rater ICC	Left	Right	Left	Right	Left	Right	Left	Right
Manual Method	0.76	0.81	0.88	0.72	0.52	0.41	0.54	0.53
Automated	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Intra-rater ICC								
Manual Method	0.78	0.66	0.88	0.73	0.71	0.79	0.87	0.77
Automated	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Conclusion: Automated segmentation of substantia nigra has improved reliability for DTI, MTR and QSM measurements. These reliable MR markers may potentially serve as objective measures of disease progression and drug effectiveness.

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