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# Segmentation of Substantia Nigra, Subthalamic and Red Nuclei with a Multi-Modal Quantitative 7T MRI High Resolution Template

A. Cabane<sup>1,2</sup>CO, A. Le Troter<sup>1,2</sup>CO, B. Testud<sup>1,2</sup>, S. Grimaldi<sup>1,2</sup>, M. Guye<sup>1,2</sup>, J-P Ranjeva<sup>1,2</sup>, L. de Rochefort<sup>1,2</sup>

CO=these authors contributed equally

<sup>1</sup>Aix Marseille Univ, CNRS, CRMBM, Marseille, France ; <sup>2</sup>AP-HM, CHU Timone, CEMEREM, Marseille, France

**Keywords:** Gray Matter, Quantitative Susceptibility Mapping, T1, high-resolution multi-modal template

**Synopsis:** The segmentation of brain substructures is very useful in the characterization of alterations involved in multiple diseases. From 200 7T brain MRI scan including MP2RAGE and MGRE used to generate quantitative T1 maps (qT1), R2\* and QSM volumes, a pipeline was developed to create a high-resolution multi-modal template at (400  $\mu\text{m}$ )<sup>3</sup> based on these multiple quantitative imaging modalities. Preliminary results show that multi-modality allows for a more precise parcellation of the SN, RN and STH substructures.

**Introduction:** The importance of high spatial resolution in-vivo 7T MRI for deep grey nuclei (DGN) segmentation has been highlighted in recent studies. The parcellation of substructures would enable easier small alteration characterization, such as in Parkinson's disease mainly affecting the Substantia Nigra (SN) [1], [2], a region adjacent to Red (RN) and Subthalamic (STH) nuclei. Multiple atlases for these areas have been proposed, such as the CIT168 atlas [3], that offers a probabilistic subdivision of SN into two parts performed from a T1-w/T2-w multi-modal (MM) template, an atlas of Zona Incerta [4] and adjacent structures that includes the SN, RN and STH, and more recently the *7TAMIBrain<sub>DGN</sub>* high-resolution (500  $\mu\text{m}$ )<sup>3</sup> DGN atlas [5]. These methods rely on the creation of templates that improve CNR and SNR via the use of super-resolution [6]. Others authors [7], [8] have shown the relevance of quantitative imaging (QSM [9] in particular) and multi-modal clustering of SN, RN and STH, for automatic segmentation by template-to-subjects co-registrations.

In this study, we introduce the *7TAMIBrain<sub>qT1\_R2\*\_QSM\_400</sub>* MM template, an improved version of *7TAMIBrain<sub>T1w\_30</sub>* [5], that is built using a larger number of subjects (30 to 200), with a higher super-resolution target (400  $\mu\text{m}$ )<sup>3</sup>. Moreover, we also propose an automatic parcellation process of the SN using multi-class clustering on the QSM template, with a segmentation on the subject space optimized by the use of an atlas-based MM co-registration.

**Methods:** 200 healthy subjects and patients with Parkinson's disease, Epilepsy, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, and Alzheimer were included. The data were acquired at 7T (Magnetom investigational device, Siemens, Erlangen, Germany) using a 1Tx/32Rx head coil (Nova Medical, Inc., Wilmington, MA USA). MP2RAGE were acquired for T1-weighted (T1-w) volume and quantitative T1 maps (qT1) (TA = 10.12 min; TR = 5000 ms; TE = 3.13 ms; inversion times T11/ T12 = 900/2750 ms; flip angles  $\alpha_1/\alpha_2 = 6/5$ ; acceleration factor GRAPPA = 3; FOV = 240 mm; voxel size = (600  $\mu\text{m}$ )<sup>3</sup> isotropic; 256 sagittal partitions (partial Fourier 6/8)). For R2\*/QSM, a transverse 3D multi-gradient echo (MGRE) sequence was applied (TR = 28ms/TE<sub>1</sub> = 2.82 ms/dTE = 4.36 ms, 600  $\mu\text{m}$  isotropic resolution, Tacq = 12.2min, BW=347Hz/pix, matrix size 320x260x256, acceleration factor 2, elliptical scanning). Phase image combination was ensured using the first-echo individual coil images as a reference. Magnitude and phase DICOM images were sent to a DICOM node for post-processing. QSM reconstruction involved a field inhomogeneity calculation and unwrapping step from the multiple echoes, a brain extraction step, an estimation of the internal field and the final MEDI reconstruction as in [10].

**Template construction:** For the creation of the multi-modal template, we relied on an iterative *SyGN* pipeline [11] (using `antsMultivariateTemplateCreation2.sh`) pooling on qT1, R2\* and QSM.

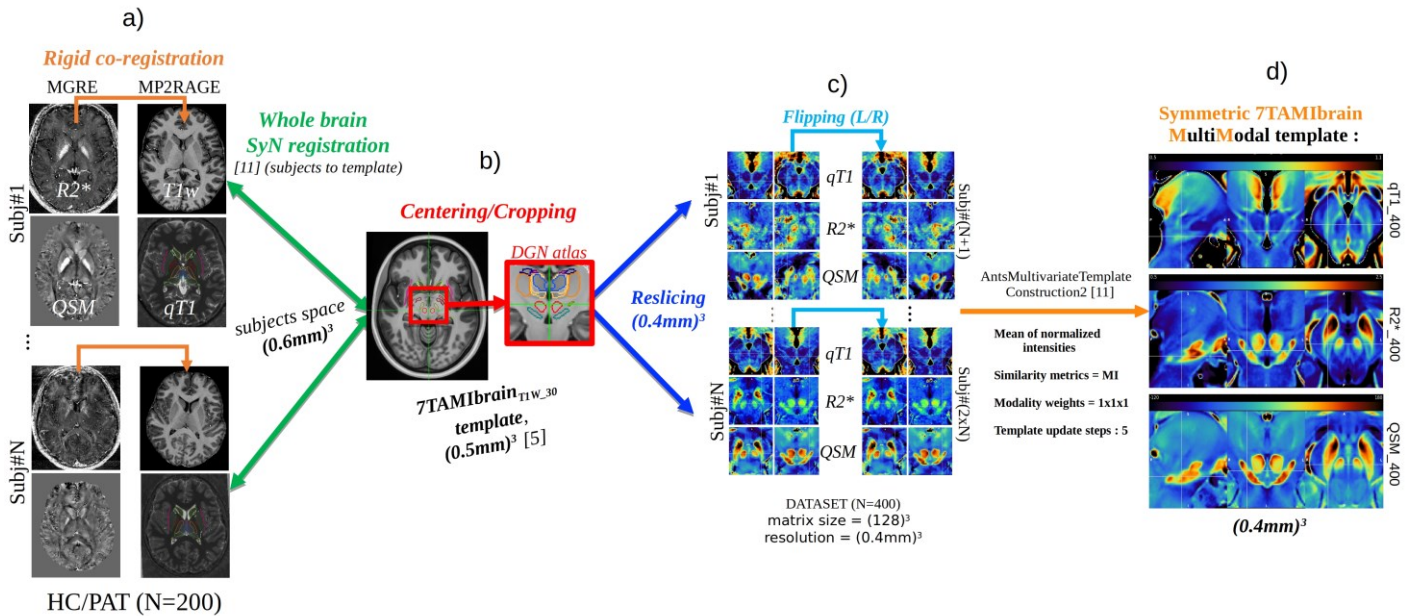
T1w volumes were initially co-registered on the *7TAMIBrain<sub>T1w\_30</sub>* template, with the parameters described in [5] and upsampled at an isotropic voxel size of (400  $\mu\text{m}$ )<sup>3</sup> cropped in the matrix of size (96)<sup>3</sup> centered on the Red Nuclei. The QSM and R2\* volumes were co-registered to the (T1w, qT1) volumes rigidly. All volumes were left/right flipped to generate by averaging a symmetric multi-contrast template (Figure 1c). A final stage of the *SyGN* process with 5 iterations was performed, using equal weights for the 3 modalities. The *7TAMIBrain<sub>qT1\_400</sub>*, *7TAMIBrain<sub>R2\*\_400</sub>*, *7TAMIBrain<sub>QSM\_400</sub>* obtained are displayed using a look-up table optimized to improve the contrast range in the SN (colored in Figure 1d, and grayscale in Figure 2a).

**Segmentation of SN/RN/STH:** We used a finite mixture modeling approach [8] (Atropos from the ants toolkit) for the segmentation of the *7TAMIBrain<sub>QSM\_400</sub>* template into four regions, RN, STH, and two parts for SN, corresponding to SNr (pars reticulata) and SNc (pars compacta). We used the CIT168 atlas as the prior probability mapping with a spatial regularization using Markov random fields (smoothingFactor=0.1, radius = 1x1x1). Two distinct registrations methods were then used, a SyN registration from the QSM template to a QSM subject (Figure 2d) and a multi-modal SyN registration on QSM, R2\* and qT1 using equals weights to compute the similarity metric. (Figure 2e).

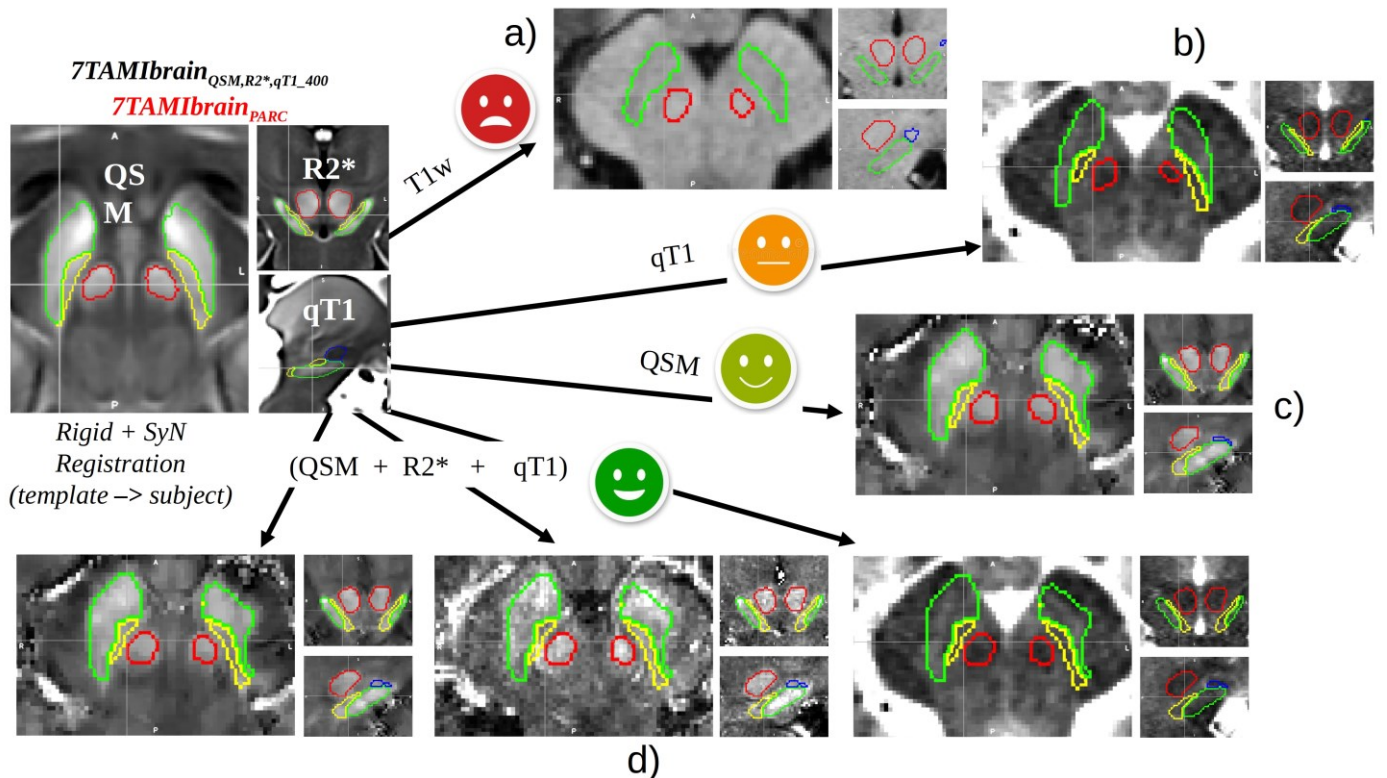
**Results and Discussions:** The creation and usage of a multi-modal template allows for a more accurate segmentation of the SN, RN and STH (figure 2e), as opposed to a T1w based segmentation that show high uncertainties at the boundaries of these regions (Figure 2b). Fine SN substructures and details are strongly highlighted on the MM template, in particular on R2\* and QSM.

**Conclusions:** In this study, a new pipeline for the generation of a multimodal template at 7T at (400  $\mu\text{m}$ )<sup>3</sup> based on quantitative T1, R2\* and QSM was presented. We also highlighted the preliminary impact and complementarity of all contrasts in helping to identify the two sub-parts SNc and SNr in the template space and their best deformation to obtain more accurate segmentation of neighboring structures such as RN, STH in the QSM subject space.

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**Figure 1** – Multimodal template construction, subject volumes (a), 7TAMIBrain<sub>T1w\_30</sub> template (b), reslicing and flipping in the subject space (c) and Multi-Modal template qT1, R2\* and QSM (d)



**Figure 2** – Segmentation of substructures in the substantia nigra, parcellation in the template space (a), segmentation in the subject space using a co-registration to the T1w volume (b), qT1 (c), QSM (d) and using the multi-modality (e)

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