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# Atlas Optimization for Deep Brain Stimulation

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**Abstract.** Electrical stimulation of the deep parts of the brain is the standard answer for patients subject to drug-refractory movement disorders. Collective analysis of data collected during surgeries are crucial in order to provide more systematic planning assistance and understanding the physiological mechanisms of action. To that end, the process of normalizing anatomies captured with Magnetic Resonance imaging across patients is a key component. In this work, we present the optimization of a workflow designed to create group-specific anatomical templates: a group template is refined iteratively using the results of successive non-linear image registrations with refinement steps in the basal-ganglia area. All non-linear registrations were executed using the Advanced Normalization Tools (ANTs) and the quality of the normalization was measured using spacial overlap of anatomical structures manually delineated during the planning of the surgery. The parameters of the workflow evaluated were: the use of multiple modalities sequentially or together during each registration to the template, the number of iterations in the template creation and the fine settings of the non-linear registration tool. Using the T1 and white matter attenuated inverse recovery modalities (WAIR) together produced the best results, especially in the center of the brain. The optimal numbers of iterations of the template creation were higher than those from the literature and our previous works. Finally, the setting of the non-linear registration tool that improved results the most was the activation of the registration with the native voxel sizes of images, as opposed to down-sampled version of the images. The normalization process was optimized over our previous study and allowed to obtain the best possible anatomical normalization of this specific group of patient. It will be used to summarize and analyze peri-operative measurements during test stimulation. The aim is that the conclusions obtained from this analysis will be useful for assistance during the planning of new surgeries.

**Keywords:** Deep Brain Stimulation (DBS), Patient normalization, Atlas, Optimisation, Registration, movement disorders

## 1 Introduction

Deep Brain Stimulation (DBS) is the most common solution for the management of symptoms of drug-refractory movement disorders such as Parkinson’s disease (PD), essential tremor (ET) or dystonia. Electrical stimulation is delivered via an electrode implanted in the movement regulation part of the brain. The complexity and precision involved in the surgical act of implanting those electrodes and the lack of understanding of the exact mechanisms of action of DBS could be approached by statistical analysis of correlation between electrical stimulation and anatomical structures in many patients. To that end, anatomical normalization of several patients into a common reference space where the analysis can be conducted has been an intense topic of research in the last 15 years [8, 3, 11]. We recently participated to this effort [13] by comparing several non-linear normalization tools with different settings, in a deep-brain focused iterative multi-modality atlas creation pipeline. The study was however limited to the evaluation of non-linear registration tools and does not include the evaluation of the influence of finer settings of the normalization pipeline itself. In the present work, we present the optimization of the normalization process by evaluating: two different methods to take advantage of the two MR image types available, the influence of the number of iterations in the atlas creation process and the optimization of the non-linear registration settings themselves.

## 2 Method

### 2.1 Clinical Data

The data used in this study originates from the University Hospital of Clermont-Ferrand, France and consists of a group of 19 patients (age: 50-84) who underwent DBS surgery (ethics approval: 2011-A00774-34/AU905). Six of those patients were admitted for ET and 13 were admitted for PD. All ET patients and two of the PD patients received electrodes in the ventro-intermediate nucleus (VIM) while the remaining 11 PD patients received electrodes in the sub-thalamic Nucleus (STN). Planning of the surgery was performed based on preoperative stereotactic T1 and WAIR (white matter attenuated inverse recovery [7]) MRI and CT. During planning, anatomical structures



**Fig. 1.** 3D visualization of the result of the manual segmentation of structures of the deep brain of relevance for the implantation of a DBS system in the STN.

in the deep brain were manually segmented (labeled) by the neurosurgeon depending on the target selected based on the symptoms. A 3D visualization of the result of segmentation is presented in Figure 1. Extensive description of the surgical procedure can be found in [12].

## 2.2 Normalization Pipeline

The normalization process consists of three steps and is based on [2]. Firstly the images of all patients are aligned with a 12 degrees of freedom transformation to the 6<sup>th</sup> generation MNI152 T1 template [5] using FSL’s FLIRT [10]. This allows the creation of an initial reference representing the group. The second step is an iterative non-linear normalization: the full brain image set from each patient is registered to the current reference, the group reference is then updated based on the result, and the process is repeated a variable number of times ( $N_{iter}$ ) whose influence was investigated in this work. Lastly, the iterative non-linear normalization is repeated using only a volume of interest in the center of the brain. All non-linear registrations were conducted using ANTS-SyN [1]. A detailed description of the normalization process can be found in [13].

## 2.3 Normalization Assessment

Along each normalization step, the anatomical structures segmented by the neurosurgeon for each patient were transformed to the target reference space. The spatial agreement across patients on the location of each anatomical structure in the template space was used as indication of the quality of the normalization. This agreement was measured by means of the Dice coefficient (DC) and the mean surface distance (MSD). The results are presented as violin plots with the average marked with a horizontal line. Each iteration of the template creation for each experiment results in a violin. Statistical significance between each sample was measured using ANOVA testing and the p-values are reported. The results were filtered for the following structures: substantia nigra, the medial thalamus (Thal\_Med), the red nucleus, the putamen, the mammillary body, the STN, the antero-lateral nucleus (AL), the dorso-lateral thalamus and the antero-lateral thalamus.

## 2.4 Parameters Exploration

In this work, the parameters from the normalization pipeline that were left to their default values in [13] were evaluated. First, two methodologies to take advantage of the two types of MRI datasets available for each patient were explored. Secondly, the number of refresh iterations in each of the non-linear template creation stages ( $N_{iter}$ ) was investigated. Third, the settings used for ANTS during the refinement steps in the deep brain were modified in order to optimize the quality of the normalization.

**Multi-modality versus Mixed-modality** The performance of the template creation was compared when using the different MRI modalities available (T1 & WAIR) separately (multi-modality) or using them together (mixed-modality) for each step of the non-linear atlas creation. The multi-modality approach uses only the T1 modality to guide the registration algorithm for full-brain normalization iterations and only the WAIR modality for the deep-brain normalization iterations. On the other hand, with the mixed-modality method, both T1 and WAIR are used together for both iterative normalization steps. The deformation obtained by registering each modality to its respective reference are then averaged and the resulting warp is used to update the template for each modality. The multi- versus mixed-modality experiment was combined with the experiment described in the next paragraph. In both cases, the *High variance* settings from [4] for ANTS were used and all 19 patients were included in the template.

**Number of Template Refresh Steps** With this experiment, the number of iterations in each of the two iterative non-linear template creations was investigated. Both full and deep brain template creations were run with the double number of iterations ( $N_{iter}^{full} = 8$ ) than the values used previously [13]. The best result for each approach (multi-modality:  $Labels_7^{full}$ , mixed-modality:  $Label_5^{full}$ ) were then used as the starting point for the deep-brain focused multi-modality and mixed-modality atlas creation.

**Non-linear Registration Settings** For this comparison, the baseline settings are the *high variance* setting from [4] that were used in the two previous evaluations. Two parameters from these settings were modified: the iteration count for the non-linear registration during the optimization stages and the convergence threshold for this optimization. Table 1 lists the different settings experimented: the *High Variance* is the baseline setting, the *fourStage* setting has the iteration count changed in order to enable the fourth stage of the optimization, the *strictThreshold* setting has a threshold for convergence smaller than the baseline setting by three decades and the *fourthStage-strictThreshold* combines those two modifications. The influence of those settings was investigated for the deep brain focused part of the normalization with ( $N_{iter}^{deep} = 8$ ) in the mixed-modality method.

## 3 Results

### 3.1 Parameters Exploration

**Multi-modality versus Mixed-modality, Number of Template Refresh Steps** The results of the template creation using multi modality and mixed modality for the full brain iterations are presented in Figure 2 and Table 2. In the case of the multi-modality approach, the best results were obtained after the 8<sup>th</sup> iteration ( $Labels_7^{full}$ ), with a mean DC of 0.687 and mean MSD of 0.720 mm.

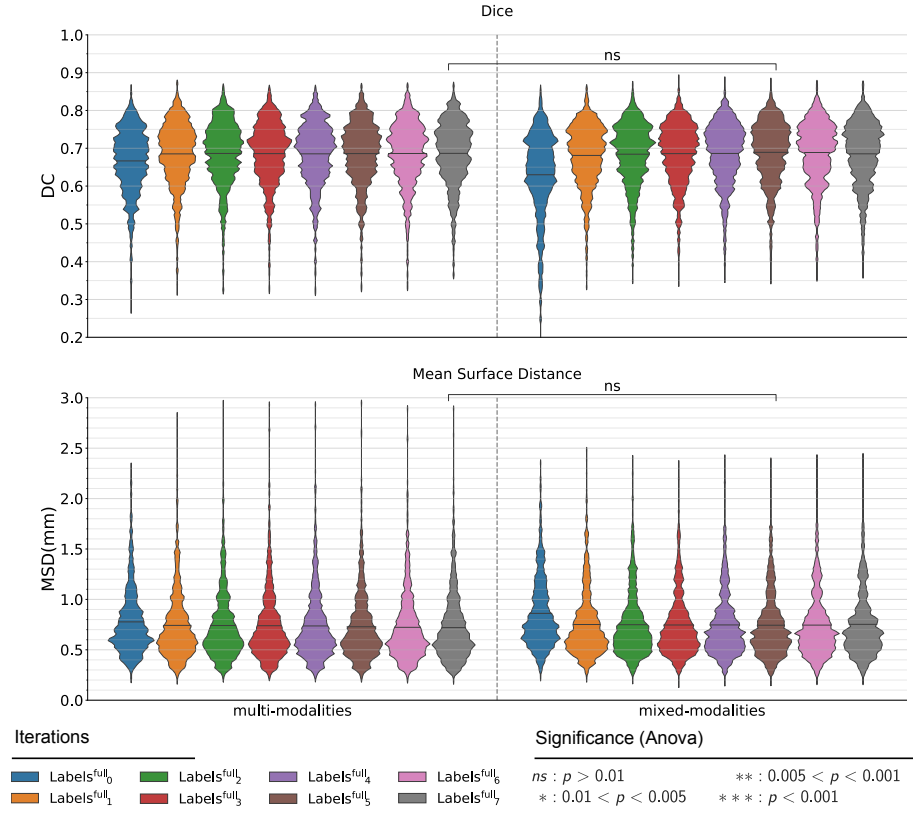
Option	High Variance	fourStage	strictThreshold	fourStage-strictThreshold
Transformation Model			SyN	
Metric			CC	
Shrink Factor			8,4,4,1	
Smoothing sigma			4,3,1,0	
Radius			4	
Transform Parameters			0.3,1,0	
Iterations count	1000, 500, 250, 0	1000, 1000, 1000, 1000	1000, 500, 250, 0	1000, 1000, 1000, 1000
Convergence Window Size			7	
Convergence Threshold	1e-6	1e-6	1e-9	1e-9

**Table 1.** List of the different set of settings experimented with ANTS. *High Variance* settings from [4].

For the mixed-modality method the results from the 6<sup>th</sup> ( $Label_5^{full}$ ) iteration results were the best, with a mean DC of 0.689 and mean MSD of 0.744mm. The difference between those two sets of results was non-significant in both DC and MSD.

The results for the iterative template creation focused on the deep brain are presented in Figure 3 with average DC and MSD values reported in Table 3. For both experiments the first iteration ( $Label_0^{deep}$ ) provides the best DC values: 0.706 and 0.715 for the multi-modality and the mixed-modality approach, respectively, with the second outperforming the first. In the case of the MSD, the values for all iterations are higher for the multi-modality approach than for the mixed-modality approach. This effect increases with successive iterations, as the MSD values worsen (increase) for the multi-modality approach while they improve (decrease) for the mixed-modality approach. The differences in DC between the best result for each experiment show strong significance with p-values under 1e-3. On the other hand, the MSD does not present significant difference between the two experiments. Despite the full-brain atlas creation not showing a clear advantage for one method over the other, in the case of the deep-brain focused iterations, the mixed modality method provides better results, and more importantly higher progression margin. As a result, the mixed-modality approach is selected for the rest of the study.

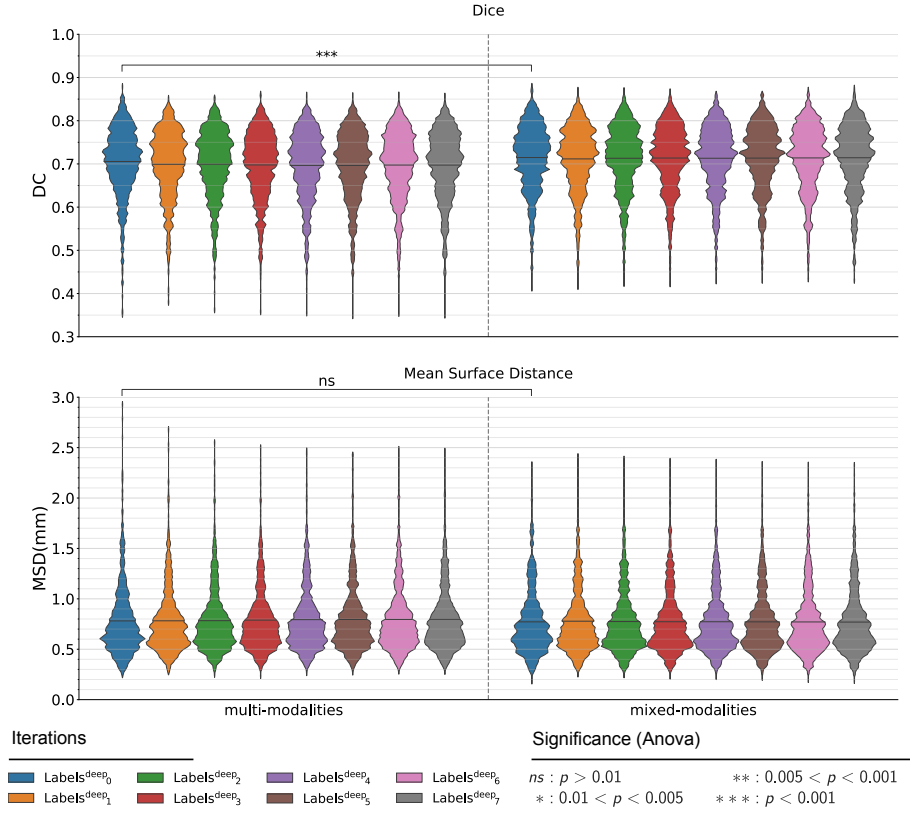
**Non-linear Registration Settings** The DC and MSD results comparing the performance of the template creation with different variations of settings are presented in Figure 4 and Table 4. The first experiment (High Variance) presented is the result from the previous section and represent the baseline settings. In this case, the best results were achieved after the first iteration with a mean DC of 0.715 and MSD of 0.772mm. The results with the *fourthStage* settings produced the best results after 6<sup>th</sup> iterations ( $Labels_5^{deep}$ ) with a DC of 0.734 and MSD of 0.713mm. These results are better than those from the baseline setting and present a strongly significant difference in both DC and MSD. In the third experiment (*strictThreshold*), the 8<sup>th</sup> iteration ( $Labels_7^{deep}$ ) provided the best results with a DC of 0.715 and MSD of 0.765mm. These results showed



**Fig. 2.** Dice coefficient and Mean Surface Distance for the full-brain template creation step using both the multi-modality and mixed-modality approaches. Results presented as violin plots with bandwidth of 0.05.

DC (MSD)	Experiment	
	multi-modality	mixed-modality
Iteration		
$Labels^{full}_0$	0.667 (0.777)	0.630 (0.861)
$Labels^{full}_1$	0.685 (0.742)	0.681 (0.751)
$Labels^{full}_2$	0.686 (0.741)	0.684 (0.749)
$Labels^{full}_3$	0.686 (0.739)	0.686 (0.746)
$Labels^{full}_4$	0.685 (0.737)	0.686 (0.747)
$Labels^{full}_5$	0.686 (0.729)	<b>0.689 (0.744)</b>
$Labels^{full}_6$	0.686 (0.723)	0.689 (0.745)
$Labels^{full}_7$	<b>0.687 (0.720)</b>	0.685 (0.752)

**Table 2.** Average values of Dice coefficient and Mean surface distance for the full-brain creation template for both multi-modality and mixed modality. Values in bold are the best result for each experiment.



**Fig. 3.** Dice coefficient and Mean Surface Distance for the deep-brain focused template creation step using both the multi-modality and mixed-modality approaches. Results presented as violin plots with bandwidth of 0.05.

DC(MSD)	Experiment	
Iteration	Multi-modality	Mixed-modality
Labels <sup>deep</sup> <sub>0</sub>	<b>0.706 (0.781)</b>	<b>0.715 (0.772)</b>
Labels <sup>deep</sup> <sub>1</sub>	0.699 (0.782)	0.712 (0.778)
Labels <sup>deep</sup> <sub>2</sub>	0.699 (0.783)	0.713 (0.775)
Labels <sup>deep</sup> <sub>3</sub>	0.698 (0.789)	0.714 (0.773)
Labels <sup>deep</sup> <sub>4</sub>	0.697 (0.794)	0.713 (0.773)
Labels <sup>deep</sup> <sub>5</sub>	0.696 (0.795)	0.713 (0.772)
Labels <sup>deep</sup> <sub>6</sub>	0.697 (0.795)	0.714 (0.771)
Labels <sup>deep</sup> <sub>7</sub>	0.697 (0.797)	0.714 (0.770)

**Table 3.** Average values of Dice coefficient and Mean surface distance for the deep-brain focused creation template for both multi-modality and mixed modality. Values in bold are the best result for each experiment.



a difference of no significance compared to the baseline settings. Lastly, for the *fourthStage-strictThreshold* setting the 7<sup>th</sup> iteration ( $Labels_6^{deep}$ ) provided the best results with a DC of 0.734 and MSD of 0.712mm. These results differ from the baseline settings with strong statistical significance.

### 3.2 Best template created

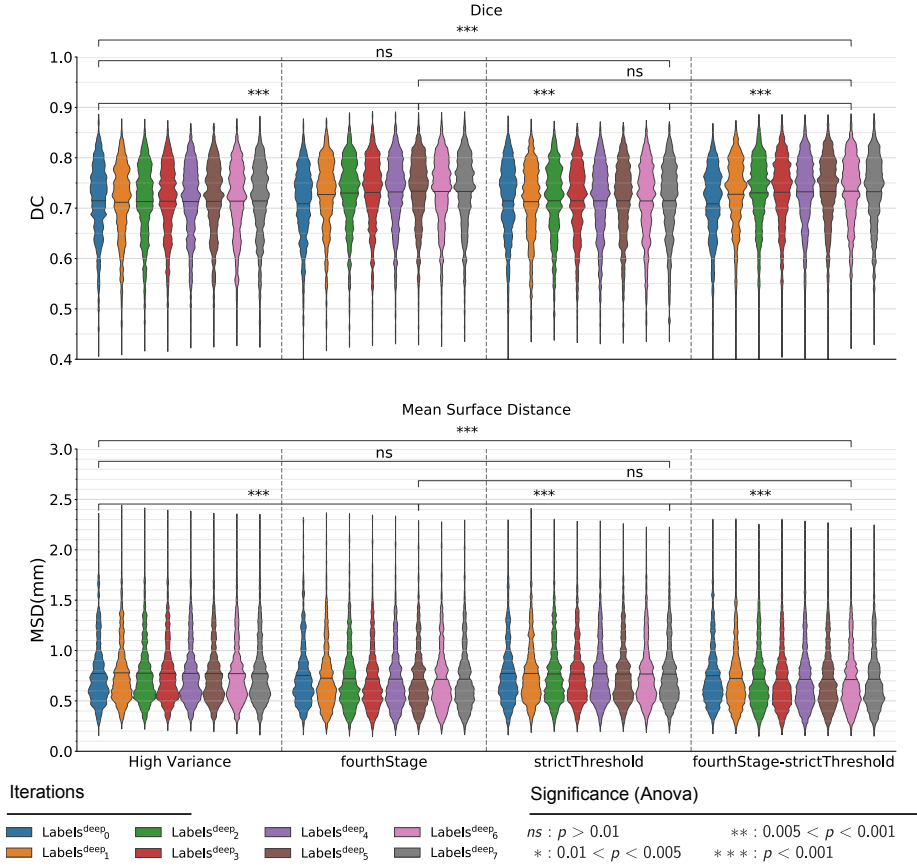
Based on the results described in the previous paragraphs, the best combination of settings identified is the following:

- Mixed-modalities approach.
- 6 template refresh steps in the full brain.
- The High variance settings for whole-brain registrations.
- 7 template refresh steps in the deep brain.
- The *fourthStage-strictThreshold* setting for registrations in the deep-brain.

Figure 5 presents the DC and MSD values for the best template created in our previous study [13]: the Multi-modalities HighVariance -  $Labels_0^{deep}$ , together with the corresponding results for the best combination of settings identified: Mixed-modalities *fourthStage-strictThreshold* -  $Labels_5^{deep}$ . The modifications on the different parameters of the workflow result in an increase in DC and decrease in MSD for all the anatomical structures considered. In order to provide a visual representation of the result of this study, a coronal slice of the best template created ( Mixed-modalities *fourthStage-strictThreshold* -  $Labels_5^{deep}$ ) at the location of largest cross-section of STN is presented in Figure 6.

## 4 Discussion

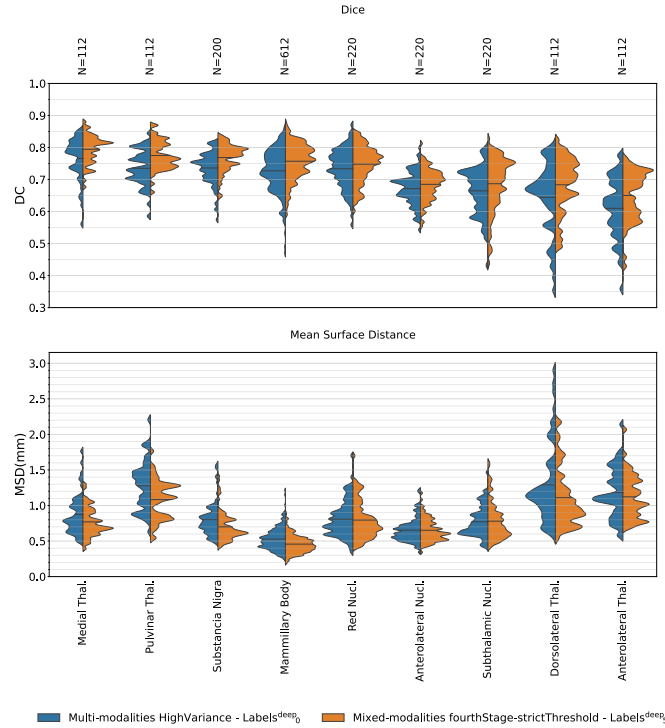
In the present study, we presented the optimization of an anatomical patient normalization workflow as well as the fine settings of the non-linear image registration software. While methods for structural normalization of patients and more specifically non-linear image registration are freely available and published in the literature, the fine settings of both of these complementary tools are an intricate issue when conducting a study on a new patient set. Klein and colleagues [6] involved the developers of non-linear registration tools themselves in order to optimize the parameters for a specific task. As a result, other studies such as [9] but also our previous study [13] reused those settings despite the different input datasets. Ewert et al. [4] proposed several sets of settings for different non-linear registration tools, but did not detail their method to optimize those. In this study, we aimed to present the optimization of the parameters in the workflow as well as the settings used for the non-linear registration tool in order to describe the influence of some of the settings. When comparing the results of the multi- and mixed-modality approaches in the full brain, none of the two showed significant advantage over the other. In the deep-brain, however, the mixed-modality method showed significantly higher DC values than the multi-modality. This corroborates the conclusion in other studies such as [4]



**Fig. 4.** Dice coefficient and Mean Surface Distance for the deep-brain focused template creation step using the *High Variance*, *fourthStage*, *strictThreshold* and *fourthStage-strictThreshold* settings. Results presented as violin plots with bandwidth of 0.05.

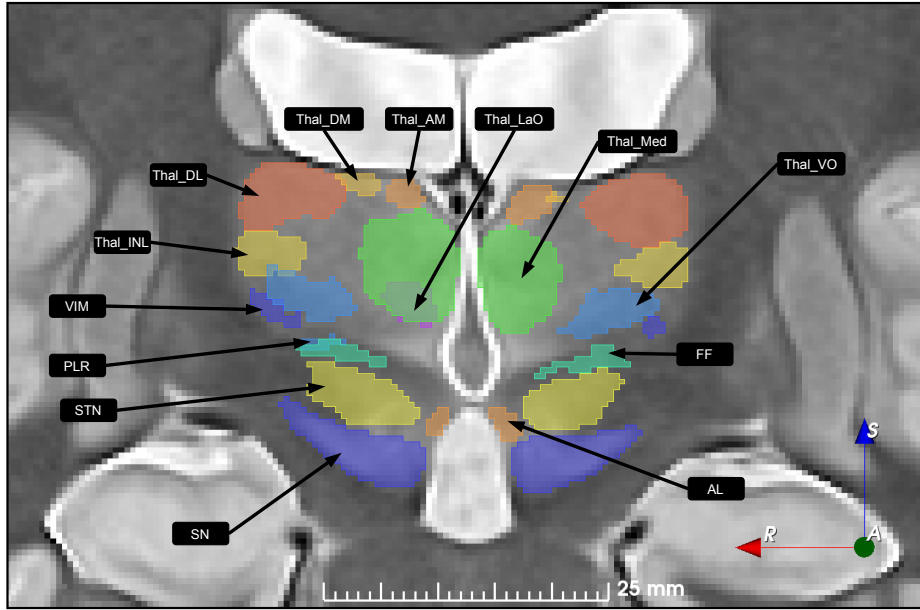
DC(MSD)	Experiment			
Iteration	High Variance	fourthStage	strictThreshold	fourthStage-strictThreshold
$Labels_0^{deep}$	<b>0.715 (0.772)</b>	0.709 (0.752)	0.714 (0.772)	0.708 (0.750)
$Labels_1^{deep}$	0.712 (0.778)	0.727 (0.726)	0.713 (0.772)	0.727 (0.723)
$Labels_2^{deep}$	0.713 (0.775)	0.730 (0.720)	0.715 (0.767)	0.730 (0.715)
$Labels_3^{deep}$	0.714 (0.773)	0.731 (0.717)	0.715 (0.768)	0.731 (0.715)
$Labels_4^{deep}$	0.713 (0.773)	0.732 (0.716)	0.714 (0.768)	0.732 (0.714)
$Labels_5^{deep}$	0.713 (0.772)	<b>0.734 (0.713)</b>	0.715 (0.767)	0.733 (0.713)
$Labels_6^{deep}$	0.714 (0.771)	0.733 (0.714)	0.714 (0.767)	<b>0.734 (0.712)</b>
$Labels_7^{deep}$	0.714 (0.770)	0.733 (0.715)	<b>0.715(0.765)</b>	0.733 (0.714)

**Table 4.** Average values of Dice coefficient and Mean surface distance for different setting in ANTS-SyN in the deep-brain. Values in bold are the best result for each experiment.



**Fig. 5.** Dice coefficient and Mean Surface Distance for the best template in [13] compared to the best settings identified from the results of the previous sections.

that combining the deformation field obtained from different modalities yields best results. The number of template refreshes showed varying results depending on the settings used by ANTS, but the general conclusion that can be drawn independently from those results is that the number of template refresh of 4 suggested in the original publication of the workflow [2] is not sufficient to reach the best result in the case of the dataset used here: in the case of the best settings (mixed-modalities, High Variance settings for full brain iterations, fourthStage-strictThreshold for the deep brain iterations) the best results were reached with 6 iterations in the full brain and 7 in the deep brain. The settings for the non-linear registration with ANTS-SyN from [4] were improved to reach higher agreement results. The activation of the fourth stage in the registration process provided higher benefits than the use of a smaller convergence threshold. This is because the fourth stage in this case is with no sub-sampling of the images thus working with original voxels. On the other hand using only the smaller convergence threshold with the fourth stage disabled does not allow to capture the details of the image because of this sub-sampling. Combining both in the fourthStage-strictThreshold setting provided marginal gains over the fourthStage setting. We however still presented the results of these settings as the best ones in the case



**Fig. 6.** Coronal slice of the template in WAIR modalities created with the best settings identified in this work. The AL, Fields of Forel (FF), ventro-oral thalamus (Thal\_VO), Thal\_Med, Oral thalamus (Thal\_LaO), Antero-medial thalamus (Thal\_AM), Dorso-medial thalamus (Thal\_DM), Dorso-lateral thalamus (Thal\_DL), Intermedio-lateral Thalamus, VIM, pre-Leminiscal Radiation (PLR), STN and SN are presented as overlay and were defined using majority voting among patients in template space.

of this study because the increase in computation time was outside the scope of this study. Readers should keep in mind that the changes in parameters in this study were conducted without considering their penalty on the processing time necessary for registrations.

## 5 Conclusion

The present article presents the optimization the process of group-specific anatomical templates focused on the deep brain. Combining several MR modalities provides better results than using them sequentially. A larger number of template refinement steps than suggested in the literature, for both in the full brain and deep-brain focused stage increased the precision of the template. The highest improvement was obtained by enabling the non-linear registration to work on the original voxel dimension after using sub-sampled versions of them. In comparison, reducing the convergence threshold in the registrations provided lower benefits. The combination of settings identified resulted in an optimized anatomical template for this group of patients, which will be used to analyse the effect of electrical stimulation in relation to the anatomy and draw conclusions that can

be generalizable to new patients, thus enabling assistance during the planning phase.

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