WHICH REGISTRATION METHOD FOR HIGH RESOLUTION FMRI TO EXPLORE HAND MOVEMENT CORTICAL REPRESENTATION ?

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ABSTRACT

Progress in our understanding of brain functions relies on our capability to explore the human cortical surface at a fine scale (typically 1.5 mm isotropic at 3T). For this purpose, high accuracy is required for all processing steps from image acquisition to data analysis. For group studies, the high inter-subject variability of the human cortices hampers their precise registration. Based on the hypothesis that function follows anatomy, accurate inter-subject sulci registration should result in precise alignment of corresponding functional regions and then improve the statistical significance of parametric maps. Converging evidence from intra-operative mapping, cytoarchitectony, and functional neuroimaging conclusively rely primary cortical regions to morphological landmarks. Thus, the so-called "hand knob" landmark, a specific feature of the central sulcus (CS), consistently separates the primary motor cortex (M1), on its anterior bank, from the primary sensory cortex (S1) on its posterior bank. In an effort to define a dedicated processing pipeline for a fine non-invasive exploration of human M1, we compared four nonlinear registration methods applied on high resolution fMRI of basic hand movements. First, based on anatomical measures, we show how recent local or global diffeomorphic techniques improve the alignment of sulcal folds in M1. Second, with functional measures, we quantitatively evaluate their effect on the detection and localization of activation clusters at the population level. Based on such measures, we show that two diffeomorphic methods working globally (DARTEL) or including sulcal constraints (DISCO+DARTEL) improve activation detection and localization opening the way to a non-invasive exploration of the human hand motor cortex.

Index Terms— Human brain, Functional MRI, Spatial normalization, Central sulcus, Realignment.

1. INTRODUCTION

A large portion of M1 is devoted to the control of hand movements. Its fine exploration using fMRI cannot be achieved without high spatial resolution image acquisition (1.5 mm isotropic at 3T) and a dedicated processing pipeline. Because of high inter-individual variability of M1, one crucial step is the quality of the inter-individual M1 realignment. M1 lies on the anterior bank of CS and extends across the precentral gyrus. On the posterior bank of the CS, lies the postcentral gyrus where primary somatosensory cortex S1 is represented. The segment of the precentral gyrus, which is shaped like a hook in the sagittal plane and an inverted omega in the axial plane (generally referred as the *hand-knob*), is a reliable landmark for identifying the CS [1] (see Figure 4). For conventional group studies, the poor cross-participant alignment of M1 leads to activation underestimation. Moreover, spatial normalization and spatial filtering, performed prior to statistical analysis to reinforce the overlap between individual activated areas, introduce *per se* a functional blurring and a loss of a precise localization of fMRI signals. This clearly hampers the separation of activated clusters found in M1. Because *hand-knob* is a good predictor of M1, we hypothesized that the combination of an accurate alignment of all *hand-knobs* of all subjects with high resolution fMRI, insuring each functional voxel to be attributed to a single gyrus, could improve the functional areas overlap and increase the significance of statistical parametric maps. For image acquisition, the improvement of spatial resolution can be achieved by decreasing plane thickness, increasing the in-plane acquisition matrix using multishot EPI sequences, and restricting the acquired volume to encompass the motor area. For spatial alignment, it is well established that linear registration is inadequate for aligning brain structures such as sulci. Several studies have compared nonlinear brain image registration algorithms working on the whole brain [2, 3], on specific regions [4], or using volume versus surface-based approaches [5]. In all these studies a set of quantitative measures was used to compare deformed structural MR source image and one target. but the effects of the registration algorithm on brain activation detection were not reported. We take a different perspective: we are mainly interested in exploring the effects of non-linear registration methods on the robustness of activation detection applied here to motor cortex investigation. For this purpose we selected a set of four recent methods that address the problem of inter-subject correspondences through different strategies and are representative of the state of the art in this active research field. The performances of the methods were quantitatively evaluated using both anatomical and

high resolution fMRI data coming from thirteen healthy control subjects. It demonstrates the clear improvement provided by large deformations registration methods applied to high resolution functional MRI on the quality of inter-individual brain structure alignment and on the detection and localization of functional activation in M1 area.

First, we considered DARTEL [6] as representative of standard diffeomorphic methods where the deformation constraints, estimated globally on the whole brain scans, align the cortical valleys and crests but without guarantee that sulci of identical anatomical denomination would be properly aligned altogether. Then, we considered DISCO+DARTEL [7] as representative of a class of methods where explicit sulcal landmarks are used to constraint the 3D deformation. Finally, we considered Diffeomorphic Demons [8] as representative of diffeomorphic methods where deformations can be estimated locally to align segmentations of specific three-dimensional region of interests (ROIs), here the *hand-knob* region. Data were also processed using the SPM8 normalization procedure widely used in the neuroscientific community.

2. MATERIAL AND METHODS

2.1. Data Acquisition and Processing

Thirteen right-handed healthy subjects (mean 27.5 y.o.) underwent a block-design fMRI protocol while performing six different tasks for each hand: extension and flexion of fingers, wrist and thumb. BOLD functional images were acquired with a high spatial resolution of $1.5\times1.5\times1.5$ mm^3 using a multi-shot EPI sequence on a 3T whole-body MR scanner (Bruker, Medspec S300). T1-weighted structural images were acquired with $1\times1\times1$ mm^3 spatial resolution using a MDEFT sequence. All functional images processing was performed using SPM8. These images were corrected for motion and very slightly smoothed using a gaussian kernel ($3\times3\times3$ mm^3). Individual statistical contrast images were realigned to the corresponding structural scan in each subject's referential. Random effects statistical group analysis was further performed after contrast images registration in a common referential using the deformation fields derived from the four registration approaches applied to the corresponding structural images. T-values associated to active clusters for each task and each realignment method were computed.

2.2. Inter-subject Registration

Individual structural images were firstly segmented and debiased using unified segmentation approach as implemented in SPM8 [9]. Then, they were registered following four different strategies and software using their own default parameters values: 1/ with mutual information registration on the MNI template (spatial normalization) using SPM8, 2/ DARTEL, 3/ DISCO+DARTEL (DiDa) and 4/ Diffeomorphic Demons (DDe) as implemented in MedINRIA toolbox[1].
–DARTEL [6] optimizes the overlap of grey and white matter tissue masks between subjects through a large deformation technique where deformations are parametrized by a velocity field that is constant in time. The algorithm embeds the construction of an average template from images of the group. The technique has been already applied in different voxel-based morphometry studies with good performances.
–The DIffeomorphic Sulcal-based COrtical (DISCO) registration explicitly enforces the alignment of identified sulci in an iterative approach. Individual sulci are first segmented and identified. An empirical template of sulci is then defined from the set of subjects before diffeomorphic transformation of each individual data onto the empirical template which is proceeded in the general framework of the Large Deformation Diffeomorphic Metric Mapping theory. Improved mask overlap and reduction of sulcal dispersion can be reached through the sequential combination of DISCO and DARTEL (DiDa), with DARTEL being initialized using DISCOs outcome [7].
–Diffeomorphic Demons (DDe) is an efficient algorithm for the non-parametric diffeomorphic registration based on the sum of squared difference in voxels intensity between images [8]. This method has been shown to outperform other techniques when applied locally to align ROIs in the medial temporal lobe [4]. To assess the influence of the reference image on the alignment quality, we applied DDe two times, with two different reference subjects R1 (DDe-R1) and R2 (DDe-R2).

3. RESULTS

3.1. Anatomical measures

To estimate the resulting cross-participant cortex overlap, we considered the intersection of registered grey matter masks restricted to ROIs designed to encompass the motor region in all individuals. We used a fuzzy union overlap metric (see [7]) computed for all pairs of subjects. For each method, we then applied the deformation field to the corresponding individual left/right CS segmented using BrainVisa[2]. The Hausdorff distances for CS between every pair of subjects were computed for each method. The mean and standard deviation of these two anatomical measures are reported in Table 1 and Fig.1 illustrates how the four methods deform locally the individual CS to align them.

As expected, the standard registration procedure used in SPM8 did not allow for a good alignment of CSs because of the strong regularization of the deformations involved in this method. On the other hand, allowing large deformations without imposing explicit anatomical constraints leads to a local mismatch between central and postcentral sulci for some subjects with DDe, with the two reference subjects. The relatively high overlap score given by DDe is made possible by

[1] http://www-sop.inria.fr/asclepios/software/MedINRIA/
[2] http://brainvisa.info

Table 1: Evaluation measures on grey matter overlap (Overlap Score) and on mean distance to the central sulcus (Hausdorff distance) for each method and hemisphere (Left Hemisphere on the left).

Method	Overlap Score (grey matter)	Hausdorff Distance (mm)	Method	Overlap Score (grey matter)	Hausdorff Distance (mm)
SPM8	0.47 ± 0.02	13.77 ± 2.92	**SPM8**	0.41 ± 0.02	12.48 ± 3.11
DARTEL	0.65 ± 0.01	9.61 ± 2.59	**DARTEL**	0.62 ± 0.01	7.85 ± 1.79
DiDa	0.59 ± 0.02	8.19 ± 2.73	**DiDa**	0.63 ± 0.02	6.31 ± 2.20
DDe-R1	0.63 ± 0.02	11.99 ± 2.86	**DDe-R1**	0.62 ± 0.02	13.12 ± 2.45
DDe-R2	0.64 ± 0.02	12.80 ± 3.27	**DDe-R2**	0.44 ± 0.02	18.54 ± 3.57

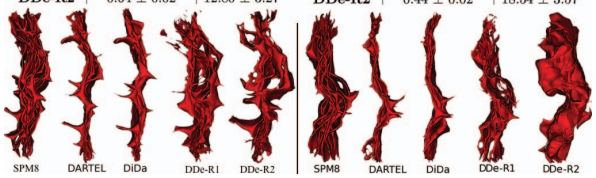


Fig. 1. Left (left) and right (right) central sulci superposition for each method.

the very low regularization of the deformations. When the alignment of CS was explicitly constrained (DiDa), we measured a clear improvement as compared to SPM8. Both DARTEL and DiDa methods provide a better superposition of the GM around the CSs with no significant difference between them. This highlights the fact that DARTEL achieves a good alignment of CS, as already observed in [3].

3.2. Functional measures

Group statistics on functional data indicate clearly that the alignment quality has a direct and strong impact 1) quantitatively on the statistical significance of the detected clusters (Figure 2) and 2) qualitatively on the activated clusters localization (Figure 4). As illustrated on Figure 2, the histograms of the T-value maps thresholded above t=5.0 ($p \leq 0.0001$ voxel level uncorrected) show that the a good sulci alignment obtained with DARTEL or DiDa provides larger activation with higher T-values than SPM8 and Demons do. Jointly with the bad superposition of CSs, Demons provide low T-values for the left and right hand flexion despite a relatively good overlap of gray-matter (Table 1 and Figure 1). Moreover, the bias induced by the choice of the reference subject appears clearly between DDe-R1 and DDe-R2. We further tested whether the four methods had significant effect on activation detectability whatever the task. We used a 2-way ANOVA followed by a Tukey-Kramer test for multiple comparisons on significant voxels ($t \geq 5$, $p \leq 0.0001$ uncorrected). This indicated that methods are different ($p=3x10^{-7}$) and are divided in two groups (SPM8, DDe-R1 and DDe-R2) and (DARTEL and DiDa) with significantly higher detectability performance for the latter (Figure 3). No statistically significant differences were found within each group. Figure 4 illustrates the localization of the main activated clusters at the group level for each method for flexion. In accordance to [10] we found with DARTEL and DiDa two main spots of activation both for flexion and extension tasks remarkably well separated for right hand (Figure 4). With SPM8 note the blurring of the mean structural image and the single large activation cluster that cannot be identified as belonging to M1. Using DDe some activations are localized on the wrong side of the sulcus bank and the double representation in M1 is not clearly elicited.

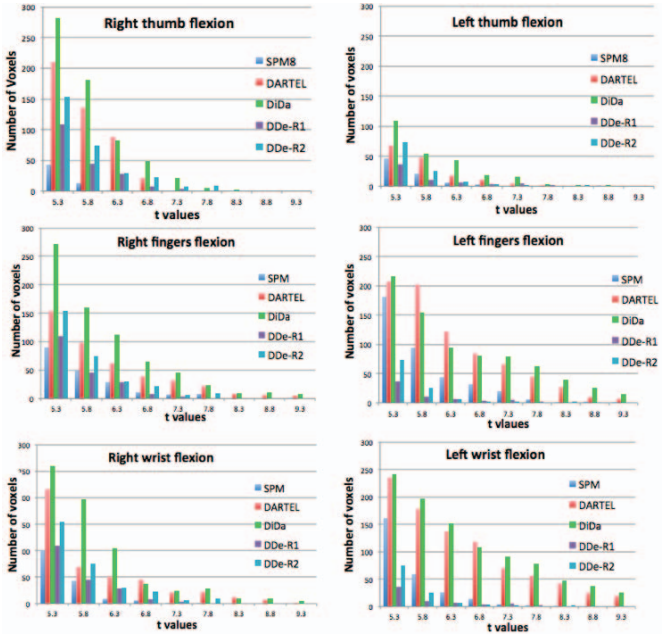


Fig. 2. Number of significantly activated voxels ($p \leq 0.0001$ voxel level non corrected) for nine bins of T-values obtained by group mean effect for flexion. Left hemisphere (left) and right hemisphere (right).

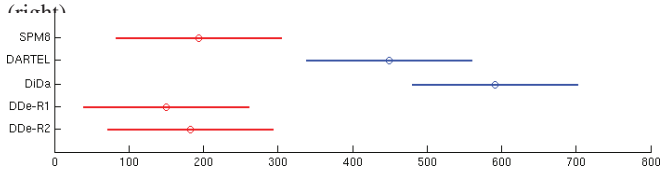


Fig. 3. Multiple comparison of means. Each group mean is represented by a circle and an interval around the circle. Two means are significantly different if their intervals are disjoint, and are not significantly different if their intervals overlap. Y axis: method, X axis: group mean.

4. DISCUSSION

Jointly to [11] or [12] for auditory cortex, our study demonstrates that the alignment quality provided by nonlinear techniques has a direct and strong impact on the functional activation detection (improvement of the statistical significance of the detected clusters) and localization (improvement of the accuracy of the clusters position). In accordance to [2, 3], anatomical measures showed that methods with high degree of freedom improve the alignment of specific brain areas and increase overlap of cortical ribbon as observed here with DARTEL and DiDa compared to SPM8 (Table 1 and Figure 1). However, in absence of explicit anatomical constraints (gray- and white- matter overlap for DARTEL and sulcal constraints for DiDa), the DDe results in unsatisfactory deformations despite relatively good measure of grey-matter

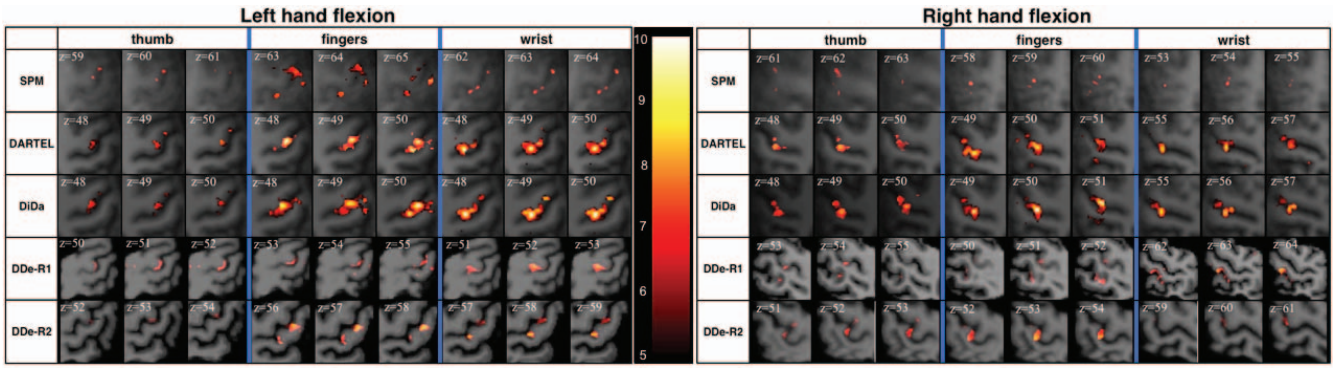


Fig. 4. Functional activation for T≥5 projected on the mean structural image obtained by each method. Three contiguous transverse slices are displayed to show for each method the largest clusters around the right central sulcus (Left) and left central sulcus (Right).

overlap. Clearly, based on functional measures and Figure 4, SPM8 and DDe can not be used to robustly detect and accurately localize hand movement cortical activation. On the contrary, based on anatomical and functional measures, DARTEL and DiDa show similar interesting performances. Despite the difference is not statistically significant, the explicit sulcal constraints introduced by DiDa seem to improve slightly the already good overlap of individual primary motor areas provided by DARTEL, showing that any change in the deformations impacts on functional group analysis. Indeed, only these two methods allow to distinguish for the first time with fMRI and without ambiguity two spots of activation in M1 for hand movements. Our study could be interestingly extended using efficient nonlinear methods such as IRTK, cortical-surface-based registration methods (e.g. FreeSurfer) or a combination of volumetric and surface registration [13]. Our results demonstrate that combining high resolution fMRI with high accuracy realignment of the central sulcus of individuals provided by DARTEL or DiDa opens the way to non invasive functional exploration of the human hand motor cortex under different normal, pathological or after rehabilitation conditions.

5. REFERENCES

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