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Combination of nonlinear registration methods with high resolution fMRI for a fine exploration of human primary motor hand area

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Abstract— **Functional investigation of human hand representation in the motor area M1 requires high resolution functional imaging, to finely separate activation in M1, and a perfect alignment of individual central sulci to improve functional areas overlap and significance of statistical parametric maps obtained from different hand movements. Based on anatomical measures, we show how recent global diffeomorphic registration techniques impact positively on the alignment of sulcal folds in M1 area. With functional measures, we evaluate their effect on the robust detection and localization of group brain activation for flexion/extension of right and left thumbs/fingers and wrists. The methodology we propose opens the way to a non invasive functional exploration of the human hand motor cortex at the group level under different normal, pathological or after rehabilitative conditions.**

I. INTRODUCTION

Group analysis of neuroimaging data requires to register anatomical and functional individual data in a common space. This spatial registration should ensure a precise alignment of individual cortical grey matter tissues. Such an alignment becomes crucial for the functional investigation of human hand representation in the primary motor cortex M1. The primary motor cortex M1 is located on the anterior bank of the central sulcus (CS) in the precentral gyrus, while the primary somatosensory cortex S1 lies on the posterior bank of the CS in the postcentral gyrus. Folding is a good predictor of cytoarchitectonics especially for primary cortex areas [1] and could thus be a good predictor of functional specialization in the primary motor cortex. The segment of the precentral gyrus, generally referred as the *hand-knob*, is a reliable landmark for identifying M1 [2]. Although, its gross organization is somatotopic, the fine functional organization of M1 remains poorly known in humans [3], [4].

In humans, the functional analysis of M1 is limited by two factors:

- insufficient spatial resolution of functional MRI (fMRI). Typical spatial resolution (3x3x3 mm^3) leads to a mixing of functional BOLD responses within M1 subregions and between M1 and S1.
- high inter-individual variability of the hand motor area. For group analysis of fMRI, the poor cross-participant alignment leads to the underestimation or the lack of activation in M1. Moreover, spatial filtering performed prior to statistical analysis to reinforce the overlap between individual active areas, introduce *per se* a functional blurring and a loss of a precise localization of fMRI signals. This clearly impedes the separation of activated clusters found in M1.

Because *hand-knob* is a good predictor of M1, we hypothesized that the combination of a perfect alignment of all *hand-knobs* across 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.

The achievement of a high spatial resolution in fMRI can be done by increasing the in-plane acquisition matrix, decreasing plane thickness and restricting the acquisition volume to the upper part of the brain encompassing the motor area. For inter-individual alignment of anatomical scans, it is well established that linear registration is inadequate for aligning cortical structures such as sulci. Several studies have compared nonlinear brain image registration algorithms working on the whole brain [5], [6], on specific regions [7], or using volume versus surface-based approaches [8]. In all these studies a set of quantitative measures was used to compare deformed structural MR source image and one target. The effects of the registration on brain activation detection was not reported. We take a different perspective: we are mainly interested in exploring the effects of nonlinear registration methods on the robustness of activation detection applied here to fine motor cortex investigation. For this purpose we selected 2 representative diffeomorphic methods, DARTEL [9] and DISCO+DARTEL [10]. Their performances were quantitatively evaluated using data coming from 13 healthy control subjects. Data were also compared with the standard procedure using the SPM8 normalization[1] widely used in the neuroimaging community.

II. MATERIAL AND METHODS

A. Data Acquisition

Thirteen right-handed healthy subjects (mean 27.5 y.o.) underwent a block-design fMRI protocol while performing 2 different movements (extension / flexion), with 3 hand parts (thumb / fingers / wrist) of the 2 hands (right dominant / left non-dominant), each separately. All along the task and rest periods, BOLD functional images were acquired with a high spatial resolution of 1.5×1.5×1.5 mm^3 obtained using

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[1] http://www.fil.ion.ucl.ac.uk/spm/

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a multi-shot EPI sequence on a 3T whole-body MR scanner (Bruker, Medspec S300). The acquisition volume covered the upper part of the brain with a repetition time of 6 seconds. A total of 222 functional volumes were acquired during 4 functional runs. T1-weighted structural images were acquired with $1\times1\times1$ mm^3 spatial resolution using a MDEFT sequence. In our experimental conditions, the measured time-serie SNR was 23, a value similar to those found at the same spatial resolution at 3T by others [11].

B. Structural Images Processing

Individual structural images were firstly segmented and debiased using unified segmentation approach as implemented in SPM8 [12]. Then, they were registered following three 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 and 3/ DISCO+DARTEL (DiDa).

1) DARTEL: Dartel [9] optimizes the overlap of grey and white matter tissue probabilistic masks between subjects through a large deformation technique where deformations are parametrized by a velocity field that is constant in time. To avoid the arbitrary selection of a single brain as a registration template, the algorithm embeds the construction of an average image template. The scheme involves iterations of DARTEL to map the scans above to their average, to form a new average. The initial smooth template become sharper each time it is re-generated, resulting in an iterative coarse-to-fine registration scheme. In the region of interest comprising the central sulcus, this method performs among the best registration techniques [6]. It has been applied in different voxel-based morphometry studies where accurate inter-subject realignment is required.

2) DISCO+DARTEL (DiDa): The DIffeomorphic Sulcal-based COrtical (DISCO) registration approach explicitly enforces the alignment of sulci in an iterative approach. Individual sulci are first segmented using BrainVisa[2] and modeled as weighted sets of points. An average sulcal template is defined as the union of the entire set of sulcal points through the group of subjects. For each sulcal label, the corresponding sulcal landmark in the template corresponds to the union of all points associated to this label for each subject. Diffeomorphic transformation of each individual data onto the empirical template is then 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 [10]. In the context of this study, a single sulcal template was computed for each hemisphere, corresponding to the central sulcus.

C. Registration Evaluation

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 [10]) computed for all pairs of subjects. For each method, we then applied the deformation field to the corresponding individual left/right CS. The Hausdorff distances for CS between every pair of subjects were computed for each method.

[2]http://brainvisa.info

D. Functional Images Processing

Functional images processing involved two steps. In a first step, individual images were computed in each subject's referential. It includes the following functional image preprocessing: a correction for motion, a registration on the structural image and a very slight smoothing using a gaussian kernel (FWHM 3mm). Individual statistical analysis was done with a single Generalized Linear Model. These computations were done with the SPM8 software. It provides a set of contrast images for each movement (extension or flexion), for each hand part (thumb or fingers or wrist) and for each hand (dominant or non-dominant). In the second step, a common referential is used to perform the group statistical analysis in a random-effect approach. Previous to the group analysis, all the individual contrast images are aligned to the common referential by applying to them the deformation fields derived from the structural images. A T-value map was thus derived for each contrast and for each realignment method. In order to compare the statistical results among these three registration approaches, the T-value maps are thresholded above t=5.0 ($p\leq0.0001$ voxel level non corrected) and their histograms are computed and compared for the three methods.

III. RESULTS

A. Anatomical measures

The registration results on the shape of the left and right CSs are displayed in Figure 1. As expected, the standard registration procedure used in SPM8 did not allow for an good alignement of CSs, compared to non-linear methods. When the alignment was locally constrained (DiDa) by relevant anatomical information, here CS delineating the M1 area, we measured only a slight improvement compared to DARTEL. This highlights the fact that DARTEL achieves a good alignment of CS, as already observed in [6]. Figure 2 quantifies the overlap of the grey matter volumes and the Hausdorff distance metric. It confirms that better alignment improves the grey matter overlap, as expected and reduces the distance of each individual's CS to the mean. Both DARTEL and DiDa methods provide a better superpimposition of the GM around the CSs with no significant difference between them.

B. Functional measures

Figure 3 displays the histograms of significantly activated voxels for flexion of left and right hands (right and left columns respectively), for the thumbs (upper row), the fingers (middle row) and the wrists (lower row). They show greater number of statistically significant voxels with

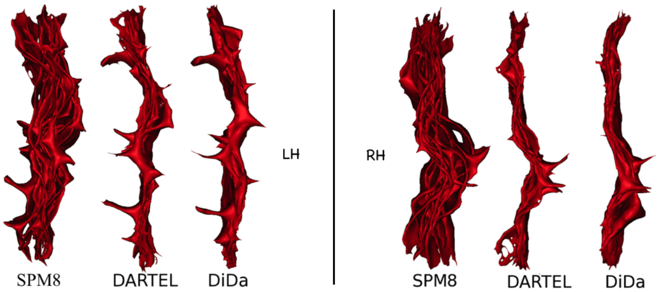

Fig. 1. Left (left) and right (right) central sulci superposition for each method.

DARTEL and DiDa as compared to SPM8. DiDa seems to improve slightly the number of activated voxels as compared to DARTEL.

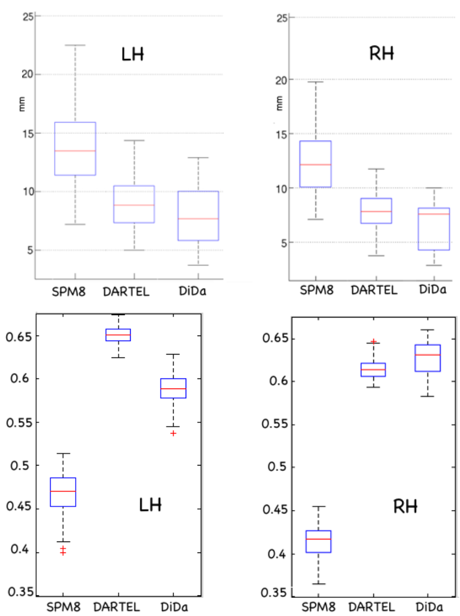

Fig. 2. Descriptive statistics of Hausdorff distance (upper row) and grey-matter tissue overlap (bottom row), obtained for the three methods. For each box, the horizontal mark indicates the median value; the upper and lower edges contain the data distribution within the first lower through the last upper quartile values; the whiskers cover values within 1.5 times this interquartile range.LH: Left Hemisphere, RH: right hemisphere

Figure 4 illustrates qualitatively the localization of the main activated clusters at the group level for each method. With SPM8 registration, we found smaller clusters, but for fingers where one spot was falsely assigned to S1. With DARTEL and DiDa, we found at least two spots of activation in the precentral gyrus, both for flexion and extension of right and left thumbs, fingers and wrists in accordance with Geyer

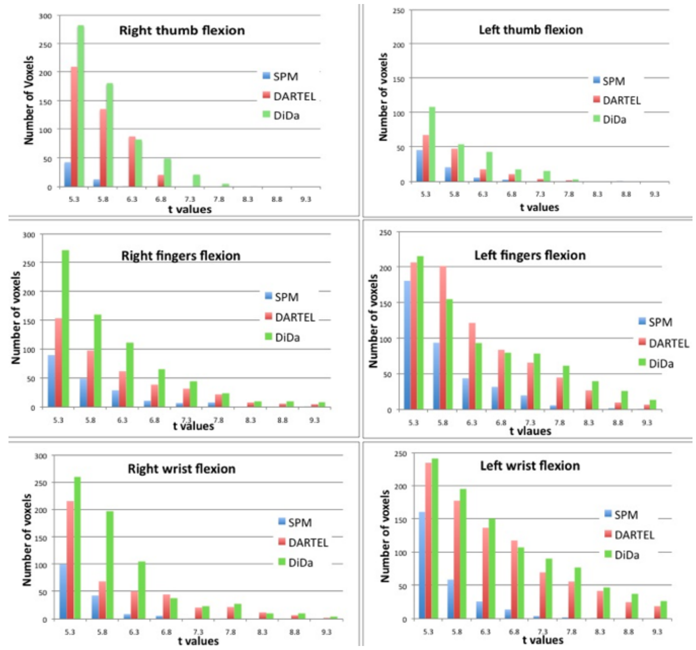

Fig. 3. Number of significantly activated voxels (P$\leq$0.0001 voxel level non corrected) for nine bins of T-values obtained by group mean effect for flexion. Left hemisphere (left) and right hemisphere (right).

[3] who found evidences of M1 subdivision (M1-4p, M1-4a).

IV. DISCUSSION

The complementarity of anatomical and functional measures indicates that both are necessary to evaluate the impact of nonlinear (here diffeomorphic) registration methods on the activation patterns. As already mentioned in [5], [6], 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 (Figure 1 and Figure 2).

While anatomical measures shows that DARTEL and DiDa have similar performances, functional measures reveal some differences (Figure 3). Indeed, small anatomical differences induced by sulcal landmarks can generate significant variations in T-values. The local constraints introduced in DiDa have in general a positive effect on T-values (see Figure 3). We focussed our study on two diffeomorphic methods because of their nice topological properties particularly relevant with high resolution fMRI. Our study could be interestingly extended using other efficient nonlinear methods such as IRTK or cortical-surface-based registration methods (e.g. FreeSurfer). Note that the use of a specific EPI template such

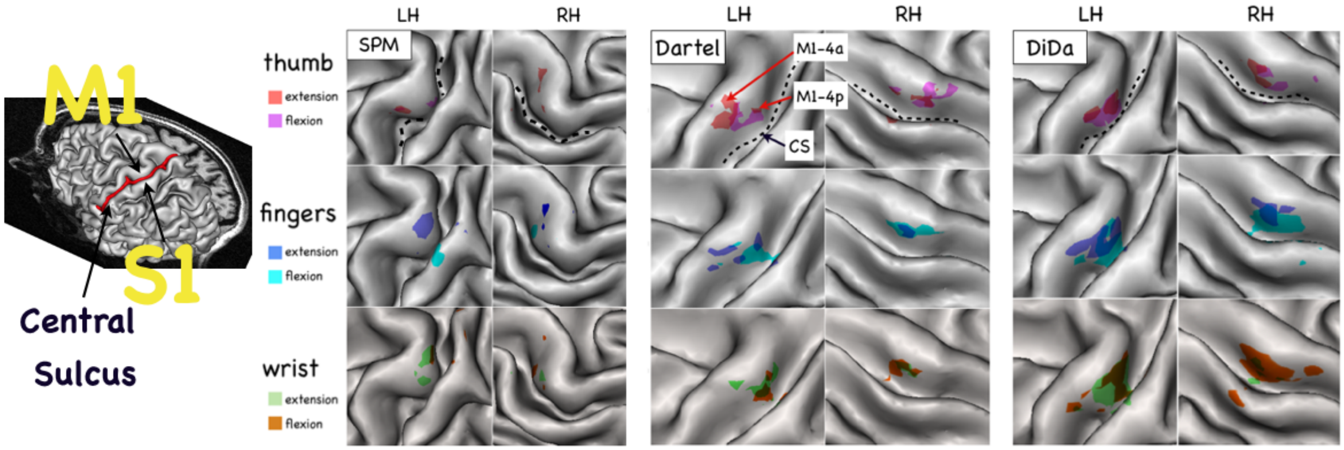

Fig. 4. Functional activation projected on the cortical surface of one subject warped on the average. Some overlap between flexion and extension activations is expected [15]. We used a T-value threshold of $\geq$5.0 (p$\leq$0.0001 voxel level non corrected).

as proposed in [13] would not allow reaching the accurate localization we search for.

V. CONCLUSION

Our study demonstrates that the alignment quality provided by nonlinear (here diffeomorphic) registration techniques has a direct and strong impact on the functional activation detection (improvement of the statistical significance of the detected clusters) and the localization (improvement of the accuracy of the clusters position). We further show that when this alignment was locally constrained by sulcal information (using DISCO), an additional improvement was achieved whereas DARTEL permits a good anatomical alignment. In the motor area studied here, this improvement is not large because DARTEL already permits a good alignment of the central sulci as was reported by Klein [6]. In other brain areas, sulcal alignment with DISCO may provide higher improvement; for instance, in the Heschl's gyrus where nonlinear deformation techniques were efficient in fMRI studies of the auditory cortex [14].

Combining high resolution fMRI with high accuracy realignment of the central sulcus of individuals obtained using non-linear registration techniques, opens the way to the non invasive functional exploration of the human hand motor cortex under different normal, pathological or after rehabilitative conditions.

VI. ACKNOWLEDGMENTS

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