35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Study of the variability of short association bundles on a HARDI database*

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Abstract— **The construction of an atlas of the human brain connectome, in particular, the cartography of fiber bundles of superficial white matter (SWM) is a complex and unachieved task. Its description is essential for the understanding of human brain function and the study of several pathologies. In this work we applied an automatic white matter bundle segmentation method proposed in the literature for the analysis of the variability of a big amount of superficial white matter bundles. The method was applied to 30 subjects of a high quality HARDI database, adding several processing steps in order to improve the results. Then we calculated some indices for studying the variability of 40 SWM fiber bundles from each hemisphere, and we constructed a model of these bundles in the MNI standard space.**

I. INTRODUCTION

The construction of an atlas of the human brain connectome [1] [2] is still an unachieved task. Long association bundles are well known but the fiber bundles of superficial white matter (SWM) have been rarely studied. This is due to their smaller size and their higher complexity, combined with their higher inter-subject variability. Their study is crucial for understanding the human brain function and structure.

Two main approaches can be used for its study. First, manual ROI placement and analyses from an expert can lead to very detailed results. In [1] a subject was studied using HARDI data and particular regions of the brain in order to study fronto-parietal association connections. Results were validated using post-mortem dissections. In addition, twelve subjects were used to evaluate the lateralization of fronto-parietal U-shaped tracts and premotor connections. A recent work, used semi-automatic segmentation of six ROIs for the study of lateralization of nine SWM tracts connecting the pre- and postcentral gyri [8]. A DTI database of ten right-handed and ten left-handed healthy subjects was used to perform a quantitative analysis on the number of fibers and volume of these short association bundles. The number of fibers was found to be larger in the left hemisphere. Second, automatic fiber labeling can be performed, in order to extend the analysis to the whole brain and a population of subjects. In [12] a non-linear gray matter and white matter ROI atlas was warped to each subject and used to segment all the bundles connecting two different cortical regions. Twenty nine SWM bundles were found in all the subjects (20 subjects) of a DTI database. This was the first work describing a big amount of short association bundles but no detailed analysis was performed about the variability of the segmented fiber bundles. Other work combined an automatic fiber clustering approach with expert labeling for the construction of an atlas of 47 SWM bundles present in at least half of the population from a HARDI database of 12 subjects [6]. This analysis was performed over the most reproducible bundles of the left hemisphere. Most of the identified bundles were already described in [12] but were subdivided into a few sub-bundles. Also, the works based on manual or semiautomatic placement of ROIs ([1], [8]) performed a precise analysis of a brain region, including bundles already described by [12] but in a more detailed level.

In order to analyze the variability of white matter bundles in both hemispheres for a big amount of bundles, in this work we applied the method proposed by [12] on a high quality HARDI database. We added some pre-processing steps in order to improve the fiber segmentation. Then we studied the variability of 40 SWM fiber bundles in 30 subjects for each hemisphere, and we constructed a model of these bundles in the MNI space. We divided the analyzed bundles into four different groups as a function of their inter-subject variability and we generated the mean 3D meshes of these bundles.

II. MATERIAL AND METHODS

A. Diffusion and Tractography Datasets

Thirty healthy subjects from a high quality HARDI database [11] were used for this analysis. Scans were acquired on a Tim Trio 3T MRI system with a 12-channel head coil (Siemens, Erlangen), and the MRI protocol included the acquisition of a T1-weighted dataset using an MPRAGE sequence (160 slices; FOV=256mm, Phase FOV=93.8%; TH=1.10mm; TE/TR=2.98/2300ms; TI=900ms; flip angle FA=9; matrix=256x240; RBW=240Hz/pixel), a B0 fieldmap, and a SS-EPI single-shell HARDI dataset along 60 optimized DW directions, b=1500s/mm^2, (70 slices; FOV 220mm, Phase FOV 100%; TH=1.7mm, TE/TR=93/14ms:

*Supported by CONICYT Chile grant, FONDECYT #11121644.
[1]The European CONNECT Project,www.brain-connect.eu
[2]The NIH Human Connectome Project,www.humanconnectomeproject.org

Label	Region	Label	Region
SPG	Superior parietal gyrus	STG	Superior temporal gyrus
CingG	Cingulate gyrus	MTG	Middle temporal gyrus
SFG	Superior frontal gyrus	ITG	Inferior temporal gyrus
MFG	Middle frontal gyrus	SOG	Superior occipital gyrus
IFG	Inferior frontal gyrus	MOG	Middle occipital gyrus
PrCG	Precentral gyrus	IOG	Inferior occipital gyrus
PoCG	Postcentral gyrus	SMG	Supramarginal gyrus
AG	Angular gyrus	PHG	Parahippocampal gyrus
PrCu	Pre-Cuneus	LFOG	Lateral fronto-orbital gyrus
Cu	Cuneus	MFOG	Middle fronto-orbital gyrus
LG	Lingual gyrus	RG	Gyrus rectus
Fu	Fusiform gyrus		

Fig. 1. List of the cortical regions of the ROI atlas used for the extraction of short associations bundles.

FA=90; matrix=128x128; RBW=1502 Hz/pixel; echo-spacing ES=0.75ms; 1 excitation; partial Fourier factor PF=6/8; parallel acceleration factor GRAPPA=2; total scan time=16min and 46s).

B. Preprocessing

The data were processed using BrainVISA/Connectomist-2.0 software [4]. They were preliminary corrected for all the sources of artifacts (eddy currents, susceptibility effects, spikes, noise) and outliers were also removed. Then, the analytical Q-ball model [3] was computed to obtain ODF fields in each voxel. Whole brain streamline deterministic tractography [10] was performed on DW native space, using a T1-based propagation brain mask computed from [5], with a forward step of 0.2 mm and a maximum curvature angle of 30. The mask was used for seeding (one seed per voxel at T1 resolution) and define the space where fibers were tracked. This lead to tractography datasets with an average of one million of fibers per subject, between 20 and 300 mm of fiber length and a maximum storing step of 5 mm. Fibers were finally filtered using an intra-subject clustering [7], in order to remove outliers, *i. e.* fibers with very low density and no packed into bundles (See Fig. 2 A)).

C. Superficial white matter bundle segmentation

We used an atlas with 130 white matter (WM) and gray matter (GM) regions of interest (ROI), created in the standard MNI space, called JHU_MNI_SS_WMPM_TypeII [9]. Following the method described in [12], this atlas was warped to each subject using dual-channel non-linear Large Deformation Diffeomorphic Metric Mapping (LDDMM) [2], preceded by a rigid transformation, using the *Diffeomap* from *MRI Studio* tools (https://www.mristudio.org/) (see Fig. 2 B)). The images used for the registration were T2-weighted and diffusion tensor fractional anisotropy (FA) images, pre-processed for skull stripping using *ROI Editor* tool. Next, 40 short association white matter fiber bundles were segmented as a function of the two cortical regions connected by each bundle. The studied bundles, described by each pair of connected regions, were defined from the analysis of previous works [12], [1], [6]. The list of cortical regions employed for the segmentation is shown in Fig. 1. The bundle

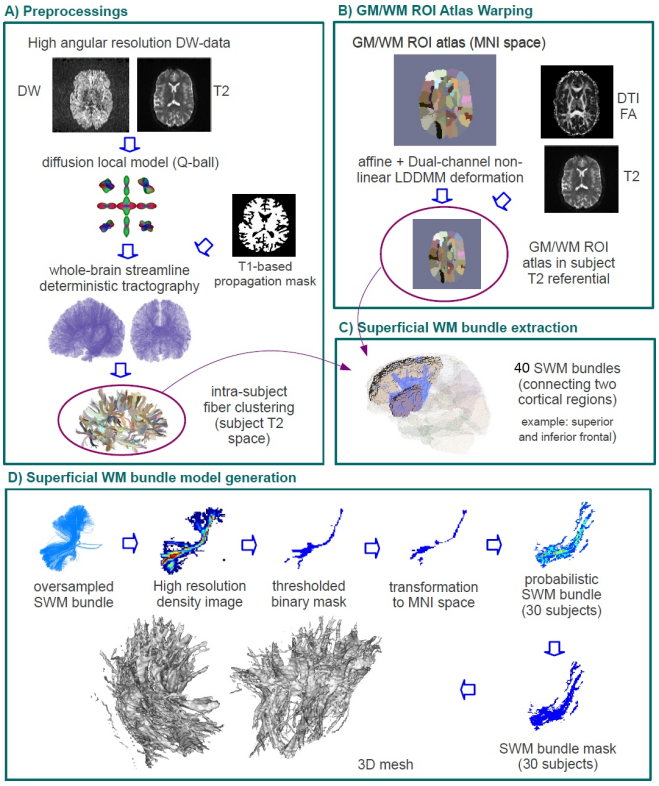

Fig. 2. A schematic of the SWM bundle model generation method.

extraction was performed separately for the right and left hemispheres. We used as input the pre-filtered fibers in order to remove outliers. A fiber oversampling was performed in order to have at least one fiber point per voxel, and a special fiber selection function was used for selecting only fibers connecting two regions and not passing through deep GM/WM structures (See Fig. 2 C)).

D. SWM bundle variability analysis

Once fiber bundles were calculated, we constructed a fiber density image of each bundle using 2x2x2 times T2-weighted image resolution (0.8594x0.8594x0.85 mm). Then, fiber bundles were binarized, keeping only voxels with more than 10% of the maximum fiber density (See Fig. 2 D)). We calculated statistics of the total number of fibers and the volume of the thresholded bundle masks. For a better comparison, the fiber number and the volume were normalized by the brain size and multiplied by the mean brain size of the thirty subjects. Binarized bundle masks from each subject where then aligned to MNI space using affine normalization. For each bundle, the corresponding masks from all the subjects were added in order to construct a bundle probability image. Finally, a 3D mesh was constructed using a binary mask of each bundle probability image (See Fig. 2 D)). Forty bundles per hemisphere were modeled using the described method.

The mean and the standard deviation (*std*) of the number of fibers (*nf*) and the volume of all the bundles (*bv*) were calculated separately for the left and right hemispheres. A factor $FC = std(nf)/mean(nf)$ was calculated in order to

Labels	FCR	FCL	SCR	SCL	VCR	VCL	VD MEAN
PrCG – PoCG	0.37	0.39	30	30	0.34	0.45	-0.07
SFG – MFG	0.39	0.42	30	30	0.45	0.48	0.00
MFG – PrCG	0.44	0.45	30	30	0.40	0.41	0.07
ITG – MTG	0.37	0.47	30	30	0.44	0.52	0.04
SFG – IFG	0.49	0.50	30	30	0.43	0.44	-0.06
IOG – MOG	0.51	0.48	30	30	0.43	0.50	0.02
STG – MTG	0.52	0.45	30	30	0.55	0.32	-0.12
STG – SMG	0.37	0.52	30	30	0.41	0.45	0.06
SFG – PrCG	0.49	0.53	30	30	0.45	0.41	-0.03
MFG – IFG	0.46	0.54	30	30	0.44	0.37	-0.09
LG – Fu	0.48	0.54	30	30	0.45	0.51	0.11
IFG – PrCG	0.49	0.55	30	30	0.52	0.45	-0.08
CingG – SFG	0.51	0.58	30	29	0.47	0.55	0.03
PoCG – SMG	0.59	0.43	30	30	0.43	0.35	-0.09
SOG – MOG	0.55	0.60	30	30	0.43	0.42	0.01
Fu – IOG	0.60	0.53	29	29	0.54	0.56	-0.04
SPG – PrCu	0.56	0.65	30	30	0.39	0.51	-0.03
SPG – AG	0.66	0.55	30	30	0.47	0.48	-0.01
Fu – MOG	0.66	0.53	30	30	0.49	0.50	-0.08
Cu – MOG	0.67	0.68	30	30	0.56	0.44	-0.13

Labels	FCR	FCL	SCR	SCL	VCR	VCL	VD MEAN
SPG – PoCG	0.70	0.54	30	30	0.63	0.47	-0.02
Cu – LG	0.71	0.61	30	30	0.56	0.50	-0.05
Fu – PHG	0.72	0.75	29	27	0.44	0.64	0.11
SPG – MOG	0.76	0.63	30	30	0.55	0.45	-0.08
CingG – PrCu	0.77	0.66	30	30	0.47	0.49	0.00
AG – SMG	0.63	0.77	30	30	0.50	0.51	0.03
PoCG – AG	0.58	0.80	30	29	0.52	0.51	0.09
AG – MOG	0.75	0.80	30	30	0.47	0.54	-0.18
Cu – SOG	0.70	0.83	30	30	0.47	0.58	-0.11
IFG – LFOG	0.73	0.83	28	30	0.55	0.44	-0.07
MTG – SMG	0.85	0.92	29	28	0.53	0.47	-0.04
LFOG – MFOG	0.94	0.93	28	28	0.55	0.53	-0.04
LFOG – RG	0.75	0.95	26	25	0.68	0.67	0.06
PoCG – MTG	0.97	0.92	23	26	0.78	0.61	-0.15
LG – MOG	1.01	1.00	29	28	0.62	0.67	0.01
PrCG – MTG	1.15	0.97	28	29	0.63	0.43	-0.19
SPG – SMG	1.25	0.63	24	30	0.62	0.44	-0.06
PrCu – SOG	1.18	1.28	28	25	0.52	0.64	0.15
SPG – SOG	1.50	0.87	28	27	0.55	0.60	0.05
SPG – CingG	1.98	1.34	12	18	1.46	1.11	-0.16

Fig. 3. Indexes of fiber bundle variability for both hemispheres. The fiber count (FC), volume count (VC) and the number of subjects were each bundle was found (SC), are listed per each hemisphere using a **R** or a **L** subindex. The mean volume count difference (VD) between both hemispheres is also listed as a measure of lateralization. Bundles are ordered as a function of their maximum FC in both hemispheres.

Group	SWM bundles (ROI1-ROI2)		FC max	SC min	VC max
1	PrCG – PoCG SFG – MFG	min	0.39	30	0.41
	MFG – PrCG ITG – MTG	mean	0.45	30	0.46
	SFG – IFG	max	0.50	30	0.52
2	IOG – MOG STG – MTG STG – SMG SFG – PrCG	min	0.51	30	0.43
	MFG – IFG LG – Fu IFG – PrCG PoCG – SMG	mean	0.57	30	0.48
	SOG – MOG SPG – PrCu SPG - AG Fu – MOG	max	0.66	30	0.55
3	CingG – SFG Fu – IOG Cu – MOG SPG – PoCG	min	0.58	28	0.49
	Cu – LG SPG – MOG CingG – PrCu AG – SMG	mean	0.74	30	0.55
	PoCG – AG AG – MOG Cu – SOG IFG – LFOG	max	0.83	30	0.63
4	Fu – PHG MTG – SMG LFOG – MFOG LFOG – RG	min	0.75	12	0.53
	PoCG – MTG LG – MOG PrCG – MTG SPG – SMG	mean	1.15	25	0.71
	PrCu – SOG SPG – SOG SPG – CingG	max	1.98	28	1.46

Fig. 4. SWM bundle classification into four groups according to their variability.

evaluate the fiber count variability, and similarly, a factor $VC = std(bv)/mean(bv)$ was calculated for the bundle volume. These indexes were calculated for all the bundles. The number of subjects where bundles were found in each hemisphere (**SC**) was also determined. Finally, the difference between right and left hemisphere volume count VC (**VD**) was calculated per each subject, using: $VD = (VC_R - VC_L)/(VC_R + VC_L)$, as an index of lateralization [1], [8].

III. RESULTS

The calculated indices are shown for both hemispheres in Fig. 3, where bundles are ordered by the maximum FC in both hemispheres (FC_R, FC_L). The name of the fiber bundles is composed by the acronyms from the two connected regions, listed in Fig. 1, as proposed by [12].

We can see that bundles present in general similar variability in both hemispheres for FC and VC. Fibers are present in almost all the subjects for both hemispheres, by the exception of the last bundle (SPG-CingG). In general, fibers with low variability are present in all the subjects. These correspond in most of the cases with the 29 bundles described in [12]. Some fibers present a high lateralization, wich in general is to the left hemisphere.

Fiber bundles were then regrouped into four groups using $FC_{max} = max(FC_R, FC_L)$ as the main index of variability. Fig. 4 lists the fiber bundles for each group, and the minimum (*min*), mean and maximum (*max*) values for FC_{max}, $SC_{min} = min(SC_R, SC_L)$, and $VC_{max} = max(VC_R, VC_L)$. A second criterion used for regrouping bundles was the SC_{min}. Group 1 contains bundles with FC_{max} between 0.39 and 0.5 and that were found in all the subjects in both hemispheres. Group 2 contains bundles with FC_{max} between 0.51 and 0.66 and that were also found in all the subjects. Group 3 contains bundles with FC_{max} between 0.58 and 0.83 and that were found in at least 28 subjects. Finally, Group 4 contains bundles with FC_{max} superior than 0.75 (and that were not found in all the subjects). The table shows in bold the bundle names of bundles that were found in all the subjects in both hemispheres. Bundles described in [1], as part of the fronto-parietal connections, are in red. These bundles were also described in [12], as the SWM bundles found in 20/20 subjects. Bundles listed in blue were only described in [12]. Fig. 5 shows the 3D meshes of the bundles for each group on a separated image.

IV. DISCUSSION AND CONCLUSION

To the best of our knowledge this is the first work that studies the variability of a big amount of SWM bundles using a HARDI database in both hemispheres. Previous works reported about the existence of these fiber bundles in a population of subjects [12] or analyzed their individual shape

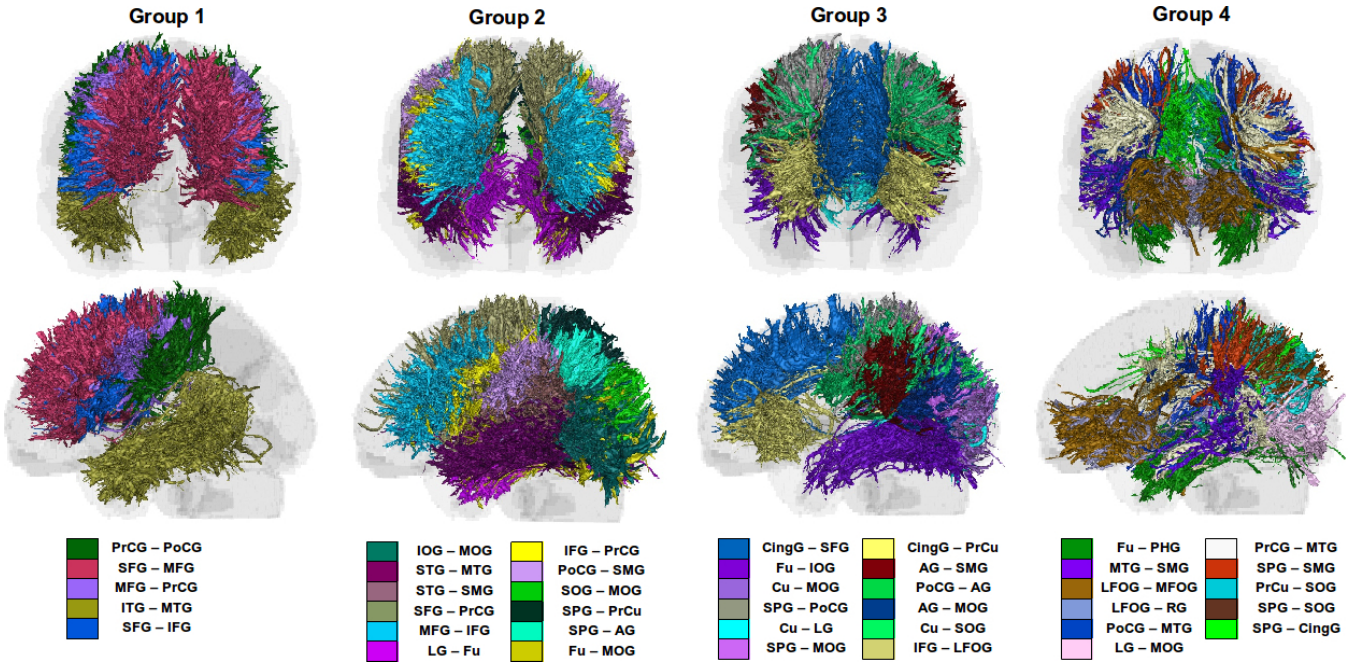

Fig. 5. Fiber bundles for the 30 subjects in MNI space, divided into 4 groups as a function of their variability. First row: Coronal view of SWM bundles for right and left hemispheres. Second row: Sagital view of SWM bundles for left hemisphere.

or variability for a restricted number of bundles ([1], [8]). We confirmed that most of the studied bundles exist in most of the subjects. Using the analyzed indexes we could classify the studied bundles into different groups as a function of their variability. For example, fiber bundles in group 1 have a low variability (for fiber count and volume), are present in all the subjects and their 3D shape seams to be better defined, as shown in Fig. 5. Most of these bundles belong to the fronto-parietal connections and were described by [1], [8] and [12]. Bundles from group 2 present higher variability than group 1 but are still present in all the subjects. In this group we found one bundle that exists in the 30/30 subjects, not described in previous studies. Fibers from groups 3 and 4 are more variable and less reproducible, in particular those from the last group. We believe that bundles with low variability, present in groups 1 and 2 can and will be used in the future for neuroscience and clinical studies, as for long association bundles, for example, for the comparison of DW indices and bundle volume between populations. Future work will be focused on the improvement of the described method and the inclusion of more subjects and more bundle subdivisions into the analysis. The feasibility of applying a better sampling of the difussion propagator, by means of more seeds per voxel or even probabilistic tractography will also be evaluated. Other registration and segmentation methods will be implemented and compared in order to determine their advantages and limitations.

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