33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Comparison between skeleton-based and atlas-based approach in the assessment of corpus callosum damages in Mild Cognitive Impairment and Alzheimer Disease

Maria Giulia Preti, Maria Marcella Laganà, Francesca Baglio, Ludovica Griffanti, Raffaello Nemni, Pietro Cecconi, and Giuseppe Baselli

Abstract—**The damage of specific bundles in the brain white matter (WM) is currently assessed in Alzheimer Disease (AD) and amnestic Mild Cognitive Impairment (aMCI) by tractography based on diffusion tensor imaging (DTI) and the consequent evaluation of diffusion parameters in reconstructed tracts. Controversial results may be due to the use of different techniques. This work aims at comparing an atlas-based technique to compute fractional anisotropy (FA) in specific tracts with the voxelwise approach of Tract-Based Spatial Statistics (TBSS). FA was evaluated in 7 portions of the corpus callosum (CC) of 10 elderly healthy controls (HC), 10 aMCI and 10 mild AD patients with both approaches. Atlas-based tractography revealed concordant results with TBSS, displaying the same significant differences between AD and HC and no significant difference between aMCI and HC. However, as regards the AD to aMCI contrast only the atlas-based method was able to find significantly lowered FA in AD in frontal and parietal CC portions. This finding shows that a proper analysis which considers a higher number of voxels, not restricting the observation to the skeleton in the assessment of CC damages, could be useful for AD to aMCI differential diagnosis and prognosis.**

I. Introduction

DIFFUSION Tensor (DT) based tractography represents a powerful tool, which allows the study of white matter (WM) integrity in the human brain *in vivo*, through the reconstruction of 3D bundle trajectories. Many studies have been published dealing with Diffusion Tensor Imaging (DTI) and tractography for the evaluation of WM damage in Alzheimer Disease (AD) and amnestic Mild Cognitive Impairment (aMCI), the transitional stage between normal cognition and AD [1]. Besides the well-known gray matter (GM) abnormalities, these conditions are characterised, in fact, by changes in the architecture and microstructure of WM fibers [2], [3], which cause consequent alterations in the anisotropy of water molecule displacements due to diffusion [4]. However, previous findings often appear controversial as to the delineation of the damage pattern in WM, particularly in MCI. Unclear results are probably due to the disuniformity in the chosen population samples (different AD state and stages), but certainly the techniques adopted in the analysis may play a significant role, as well [5]. The assessment of WM integrity is usually accomplished through the computation of Fractional Anisotropy (FA), a quantitative index obtained from the DT, quantifying the diffusion directionality [6]. Previous literature reports DTI studies on aMCI and AD based on Regions Of Interest (ROI) analysis [7]-[9], individual tractography [10]-[13], atlas-based tractography [14] and, more recently, Tract-Based Spatial Statistics (TBSS) [3], [5], [15]-[17]. FA computation in WM structures with ROI-based approaches consists in evaluating FA values within *a-priori* defined ROIs and therefore appears strongly operator-dependent and scarcely reproducible [5]. In order to assess tract-specific FA values, tractography represents an effective technique, but diffusion abnormalities in patients often compromise the individual tract reconstruction. To overcome this problem, a possible solution is provided by the use of tractographic atlases, i.e. reference patterns of tracts obtained from the average of a group of healthy controls (HC), which permit the evaluation of tract features even in pathological brains, in absence of an individual tractographic reconstruction. In this regard, a critical aspect is represented by the alignment errors within the control group or between the atlas and the pathologic brain as well as by the biological variability, which could bring to misleading results in the application to patients, due to border and partial volume effects which may include CSF or GM voxels in the statistics. Alternately, the recently introduced voxelwise analysis of TBSS [18] restricts the evaluation of diffusion parameters to a WM skeleton extracted from the FA map, rather than from a specific tract classification. This technique showed to improve the objectivity, interpretability and sensibility of multi-subject diffusion data analysis [18], also alleviating the alignment-related problems [5]. Compared to TBSS, atlas-based tractography may suffer of errors strongly depending on the registration accuracy; nonetheless, it extends the analysis to the entire tract volumes, not only to the central skeleton line, thus offering the possibility to perform a more complete evaluation in presence of a non homogeneous damage. Moreover, border effects in the atlas application may be at least partially controlled by proper erosion of tract volumes, excluding all the voxels with FA values under a determined threshold, as suggested by Reich and colleagues [19] and

Manuscript received June 17, 2011.

M. G. Preti is with the Dipartimento di Bioingegneria, Politecnico di Milano, Milano, Italy and also with the Fondazione Don Carlo Gnocchi, Milano, Italy. (corresponding author to provide phone: 0039 347 5117107; fax: 02 40308346; e-mail: gpreti@dongnocchi.it).

M. M. Laganà, F. Baglio, L. Griffanti, R. Nemni , P. Cecconi are with the Fondazione Don Carlo Gnocchi, Milano, Italy.

R. Nemni is also with the Università degli Studi di Milano, Milano, Italy.

G. Baselli is with the Dipartimento di Bioingegneria, Politecnico di Milano, Milano, Italy.

also using probabilistic weighing of the reference atlas.
The purpose of the present study was to compare a probabilistic atlas technique with TBSS in the computation of FA values in the Corpus Callosum (CC) of aMCI and mild AD patients, aiming on highlighting possible differences in the results of the two approaches.

II. METHODS

A. Subjects

Diffusion weighted images (DWI) were obtained from four groups of participants: 1) 10 patients diagnosed with aMCI according to Petersen criteria [1] (age 73.0±6.4, mini-mental status examination MMSE 26.0±1.8; 5 females); 2) 10 patients diagnosed with mild AD according to the NINCDS-ADRDA criteria [20] (age 73.4±4.9, MMSE 19.6±2.4; 5 females); 3) 10 HC (age 66.9±6.9, MMSE 28.3±1.1; 5 females); 4) 10 HC used for the atlas construction (age 65.0±8.1, MMSE 27.1±2.6; 5 females). No significant differences were found in age and gender among the examined groups. Patients were recruited at a specialist dementia clinic of the Fondazione Don Gnocchi, Milan, Italy. HC were preliminarily screened to exclude major systemic, psychiatric or neurological illnesses. The study was conformed to the ethical principles of the Helsinki Declaration and informed written consent was obtained from all subjects. Patients' T2 scans were analyzed by an experienced neurologist and excluded in presence of WM hyperintensities outside the normal range.

B. MRI Acquisitions

Brain MRI acquisitions were performed using a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany), including the following sequences: 1) dual-echo turbo spin echo (TR=2650 ms, TE=28/113 ms, echo train length=5, flip angle=150°, 50 interleaved 2.5-mm-thick axial slices, matrix size=256x256 interpolated to 512x512, FOV=250mm x 250mm); 2) diffusion weighted pulsed-gradient spin-echo planar (TR=7000 ms, TE=94 ms, 50 2.5-mm-thick axial slices, matrix size=128×96, FOV=320mm × 240 mm), with diffusion gradients (b-value=900s/mm^2) applied in 12 non-collinear directions. Two runs of images were acquired for each subject, with one b=0 image without diffusion weighting.

C. DTI Analysis

DWI were corrected for eddy current distortions using FSL (http://www.fmrib.ox.ac.uk/fsl/). Brain was extracted using the FSL Brain Extraction Tool (BET). For every subject, the two runs were registered to the same space with SPM5 (www.fil.ion.ucl.ac.uk/spm), by estimating the transformation between the b=0 image of the second run and the b=0 image of the first one and by applying it to all the DWI of the second run. The DT was estimated by using Diffusion Toolkit (www.trackvis.org) v0.6, which firstly rotates the B-matrix for slice angulation and for the rotation applied by FSL and SPM. The DT was then diagonalized, obtaining its eigenvalues and eigenvectors and from them the tensor scalar invariant FA was computed.

D. CC atlas construction

For the fourth group of participants, tractography was performed with Diffusion Toolkit, using the brute force approach and the Interpolated Streamline deterministic algorithm. An angle of 35° and an FA of 0.2 were adopted as stopping criteria. For each subject, the CC was segmented in 7 portions (CC1-CC7), using the ROI suggested in [21]. ROI were positioned on FA maps with Trackvis (www.trackvis.org) v0.5.1. Density maps of the reconstructed tracts were created. Then, FA images were nonlinearly registered to the MNI152 standard space with SPM5, using the FMRIB58_FA supplied by FSL as template image for the alignment. For each HC, the estimated transformation between his FA map and the template was applied to the tract density maps of the 7 segmented CC portions. The tract density maps were then binarised and averaged separately for each CC portion, in order to obtain maps indicating the probability of one voxel to belong to the considered tract. With the aim of increasing the certainty of belonging to the tract of interest, probability maps were thresholded above 90% probability.

E. CC FA Analysis 1: TBSS

The first FA analysis was performed using TBSS v1.2 [18], part of FSL. All subjects' FA maps were nonlinearly aligned to a 1x1x1mm standard space in MNI152 coordinates, using FSL FNIRT and the FMRIB58_FA as template image. All the aligned images were averaged together obtaining a mean FA, which was thinned to create a mean skeleton. The skeleton was thresholded at a value of 0.2 and, for every subject, individual FA data were projected into the skeleton, as detailed in [18]. Following the standard TBSS procedure, data were then fed into voxelwise statistics with following group comparisons: 1) HC vs. aMCI; 2) HC vs. AD; 3) aMCI vs. AD. The permutation tool "randomize" was used, with 5000 permutations and a significant threshold for between-group differences of $p<0.05$. The Threshold-Free Cluster-Enhancement (TFCE) was adopted as correction for multiple comparisons. The p-value images containing the significantly different voxels were masked with the 7 portions of the CC atlas, in order to highlight the differences for every CC portion separately.

F. CC FA Analysis 2: atlas-based tractography

Average FA values along the tracts in the 7 CC portions were extracted for every subject using the following atlas-based method. Mean FA value was obtained within the atlas CC portions for every subject using an in-house Matlab script, which masked the registered FA maps of all subjects (of groups 1-3) with the created atlases and computed the mean FA weighted for the probability given by the atlas at every voxel. In order to minimise the probability of CSF or GM inclusion, voxels with FA<0.2 were excluded from the computation [19]. The extracted mean FA values were

compared between groups with an ANOVA test with correction for multiple comparisons, performed using SPSS Statistics v17.0 (www.spss.com).

III. Results

The probabilistic atlas of the CC divided in 7 portions is showed in Fig. 1. As to a comparisons vs. HC, both the atlas-based approach (see Table I) and TBSS (Fig. 2) displayed significant differences in AD and non-significant differences in aMCI, in any CC section. Conversely, concerning AD vs. aMCI, the two approaches gave different results. In fact, TBSS was not able to detect any voxels with a statistically significant FA difference between the two groups. Instead, the atlas-based analysis revealed a significantly lower FA in the frontal and parietal CC regions (CC1-CC2-CC3-CC4, see Table I) of AD in respect to aMCI.

IV. Discussion

The present study compared the results of TBSS and atlas-based tractography in the assessment of CC damages in aMCI and mild AD. To our knowledge, it is the first study involving an atlas of the CC divided in 7 portions, instead of the common subdivision in three or four regions (rostrum, genu, body and splenium). This segmentation allowed a more precise localisation of the damage affecting the bundle. Moreover, the probabilistic atlas does not require tensor registration and reorientation steps, as in recently proposed approaches [22], and additionally provides robust information regarding the probability of a WM location to belong to a specific tract and allows the consequent weighing and thresholding of tract-specific DTI parameters. In concordance with our results, previous TBSS studies found out a significantly reduced FA in AD patients compared with HC, particularly in the CC genu and splenium [5], [17]. As regards the comparison aMCI vs. HC, our findings agreed with the results of [16] and of previous DTI studies [23]-[25], displaying no difference between the two groups. The significant FA reduction in AD compared with aMCI in the CC frontal and parietal portions detected with atlas-based tractography was not revealed by the TBSS analysis. This discrepancy is interesting and could reveal a higher sensitivity of the atlas-based method in the detection of differences between aMCI and AD. A possible explanation for that could be related to the different analysis performed on the tract with the two methods: a skeleton-based approach, as TBSS, evaluates only the central line of the tracts, thus ignoring their whole extent, which can be particularly important in wide spread tracts such as CC. The analysis of the tract in its entire width, instead, could reveal abnormalities in FA values and help in the distinction between patients at different stages, as it happens in the observed comparison. Thanks to the analysis of the entire bundles, in fact, it could be possible to highlight the different anatomo-pathological mechanisms of WM changes (retrogenesis and Wallerian degeneration) and, in this way, detect initial modifications between aMCI and AD.

A limit of the present comparison of atlas-based and TBSS methods is the segmentation in 7 CC ROI of the former which is absent in the latter, due to the intrinsic nature of the voxel-based TBSS. Nonetheless, in future analysis an evaluation of TBSS masked by the atlas ROI could provide a more homogeneous comparison.

The high sensitivity of atlas-based methods to misregistration artefacts compared with TBSS can be effectively controlled by means of a probabilistic definition of the atlas and the consequent limitation to high membership probabilities, and by the exclusion of all FA values under the commonly adopted threshold of 0.2 in the atlas application. However, a larger analysis including a bigger sample size should be performed to confirm the different behaviour of the two approaches. In addition, the use of different threshold values could be experimented in both methods (for the atlas application and the skeleton thresholding) and the investigation through a ROC analysis would be extremely interesting to evaluate how these values affect the results. Finally, results relevant to CC damage in AD and aMCI may not be extended to other tracts with an inherently different geometry and to other pathologies.

V. Conclusions

The performances of the two experimented techniques of CC FA analysis appeared similar for the comparisons HC vs. aMCI, and HC vs. AD, but differed in the detection of differences between AD and aMCI, where the atlas-based tractography proved to be more sensitive. Our findings showed the reliability of an atlas-based method, based on the use of a probabilistic atlas of the CC divided in 7 portions, which allows an accurate analysis of the tract in its entire extent, displaying to be probably more adapt in the study of these pathologies at the onset.

References

[1] R. C. Petersen, "Mild cognitive impairment as a diagnostic entity," *J. Intern. Med.,* vol. 256, pp. 183-194, Sep. 2004.

[2] M. Di Paola, G. Spalletta and C. Caltagirone, "In vivo structural neuroanatomy of corpus callosum in Alzheimer's disease and mild cognitive impairment using different MRI techniques: a review," *J. Alzheimers Dis.,* vol. 20, pp. 67-95, 2010.

[3] L. Serra, M. Cercignani, D. Lenzi, R. Perri, L. Fadda, C. Caltagirone, E. Macaluso and M. Bozzali, "Grey and white matter changes at different stages of Alzheimer's disease," *J. Alzheimers Dis.,* vol. 19, pp. 147-159, 2010.

[4] S. Mori and J. Zhang, "Principles of diffusion tensor imaging and its applications to basic neuroscience research," *Neuron,* vol. 51, pp. 527-539, Sep. 2006.

[5] Y. Liu, G. Spulber, K. K. Lehtimaki, M. Kononen, I. Hallikainen, H. Grohn, M. Kivipelto, M. Hallikainen, R. Vanninen and H. Soininen, "Diffusion tensor imaging and Tract-Based Spatial Statistics in Alzheimer's disease and mild cognitive impairment," *Neurobiol. Aging,* Nov. 2009.

[6] C. Pierpaoli and P. J. Basser, "Toward a quantitative assessment of diffusion anisotropy," *Magn. Reson. Med.,* vol. 36, pp. 893-906, Dec. 1996.

[7] E. J. Rogalski, C. M. Murphy, L. deToledo-Morrell, R. C. Shah, M. E. Moseley, R. Bammer and G. T. Stebbins, "Changes in parahippocampal white matter integrity in amnestic mild cognitive

impairment: a diffusion tensor imaging study," *Behav. Neurol.,* vol. 21, pp. 51-61, 2009.
[8] T. F. Chen, C. C. Lin, Y. F. Chen, H. M. Liu, M. S. Hua, Y. C. Huang and M. J. Chiu, "Diffusion tensor changes in patients with amnesic mild cognitive impairment and various dementias," *Psychiatry Res.,* vo. 173, pp. 15-21, July 2009.
[9] D. B. Parente, E. L. Gasparetto, L. C. da Cruz Jr, R. C. Domingues, A. C. Baptista, A. C. Carvalho and R. C. Domingues, "Potential role of diffusion tensor MRI in the differential diagnosis of mild cognitive impairment and Alzheimer's disease," *AJR Am. J. Roentgenol.,* vol. 190, pp. 1369-1374, May 2008.
[10] Y. Zhang, N. Schuff, A. T. Du, H. J. Rosen, J. H. Kramer, M. L. Gorno-Tempini, B. L. Miller and M. W. Weiner, "White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI," *Brain,* vol. 132, pp. 2579-2592, Sep. 2009.
[11] Y. Nakata, N. Sato, O. Abe, S. Shikakura, K. Arima, N. Furuta, M. Uno, S. Hirai, Y. Masutani, K. Ohtomo and S. Aoki, "Diffusion abnormality in posterior cingulate fiber tracts in Alzheimer's disease: tract-specific analysis," *Radiat. Med.,* vol. 26, pp. 466-473, Oct. 2008.
[12] M. Morikawa, K. Kiuchi, T. Taoka, K. Nagauchi, K. Kichikawa and T. Kishimoto, "Uncinate fasciculus-correlated cognition in Alzheimer's disease: a diffusion tensor imaging study by tractography," *Psychogeriatrics,* vol. 10, pp. 15-20, Mar. 2010.
[13] T. Taoka, M. Morikawa, T. Akashi, T. Miyasaka, H. Nakagawa, K. Kiuchi, T. Kishimoto and K. Kichikawa, "Fractional anisotropy--threshold dependence in tract-based diffusion tensor analysis: evaluation of the uncinate fasciculus in Alzheimer disease," *AJNR Am. J. Neuroradiol.,* vol. 30, pp. 1700-1703, Oct. 2009.
[14] M. Pievani, F. Agosta, E. Pagani, E. Canu, S. Sala, M. Absinta, C. Geroldi, R. Ganzola, G. B. Frisoni and M. Filippi, "Assessment of white matter tract damage in mild cognitive impairment and Alzheimer's disease," *Hum. Brain Mapp.,* vol. 31, pp. 1862-1875, Dec. 2010.
[15] L. Zhuang, W. Wen, W. Zhu, J. Trollor, N. Kochan, J. Crawford, S. Reppermund, H. Brodaty and P. Sachdev, "White matter integrity in mild cognitive impairment: a tract-based spatial statistics study," *Neuroimage,* vol. 53, pp. 16-25, Oct. 2010.
[16] J. S. Damoiseaux, S. M. Smith, M. P. Witter, E. J. Sanz-Arigita, F. Barkhof, P. Scheltens, C. J. Stam, M. Zarei and S. A. Rombouts, "White matter tract integrity in aging and Alzheimer's disease," *Hum. Brain Mapp.,* vol. 30, pp. 1051-1059, Apr. 2009.
[17] N. H. Stricker, B. C. Schweinsburg, L. Delano-Wood, C. E. Wierenga, K. J. Bangen, K. Y. Haaland, L. R. Frank, D. P. Salmon and M. W. Bondi, "Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis," *Neuroimage,* vol. 45, pp. 10-16, Mar. 2009.
[18] S. M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T. E. Nichols, C. E. Mackay, K. E. Watkins, O. Ciccarelli, M. Z. Cader, P. M. Matthews and T. E. Behrens, "Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data," *Neuroimage,* vol. 31, pp. 1487-1505, July 2006.
[19] D. S. Reich, A. Ozturk, P. A. Calabresi and S. Mori, "Automated vs. conventional tractography in multiple sclerosis: variability and correlation with disability," *Neuroimage,* vol. 49, pp. 3047-3056, Feb. 2010.
[20] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," *Neurology,* vol. 34, pp. 939-944, July 1984.
[21] C. Lebel, S. Caverhill-Godkewitsch and C. Beaulieu, "Age-related regional variations of the corpus callosum identified by diffusion tensor tractography," *Neuroimage,* vol. 52, pp. 20-31, Aug. 2010.
[22] H. Peng, A. Orlichenko, R. J. Dawe, G. Agam, S. Zhang, K. Arfanakis, "Development of a human brain diffusion tensor template," *Neuroimage*, vol. 46(4), pp. 967-980, July 2009.
[23] D. Medina, L. DeToledo-Morrell, F. Urresta, J. D. Gabrieli, M. Moseley, D. Fleischman, D. A. Bennett, S. Leurgans, D. A. Turner and G. T. Stebbins, "White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study," *Neurobiol. Aging,* vol. 27, pp. 663-672, May 2006.
[24] S. E. Rose, K. L. McMahon, A. L. Janke, B. O'Dowd, G. de Zubicaray, M. W. Strudwick and J. B. Chalk, "Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment," *J. Neurol. Neurosurg. Psychiatry.,* vol. 77, pp. 1122-1128, Oct. 2006.
[25] R. Stahl, O. Dietrich, S. J. Teipel, H. Hampel, M. F. Reiser and S. O. Schoenberg, "White matter damage in Alzheimer disease and mild cognitive impairment: assessment with diffusion-tensor MR imaging and parallel imaging techniques," *Radiology,* vol. 243, pp. 483-492, May 2007.

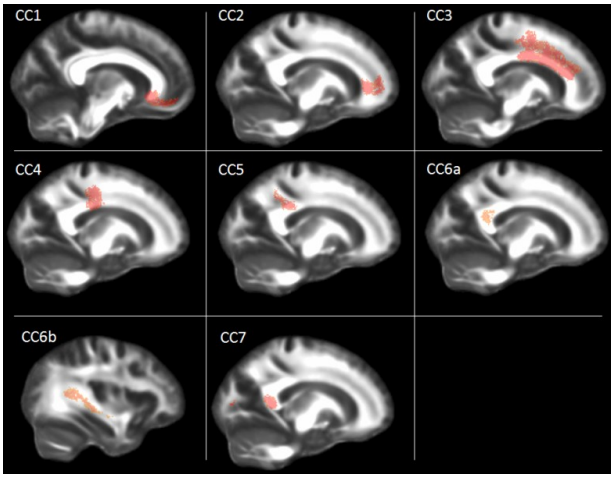

Fig. 1. CC Atlas, subdivision in 7 portions (CC1: orbital frontal, CC2: anterior frontal, CC3: superior frontal, CC4: superior parietal, CC5: posterior parietal, CC6: temporal, CC7: occipital), ROIs in the median plane. CC6 is shown both on the medial plane (CC6a) and on a lateral sagittal plane (CC6b).

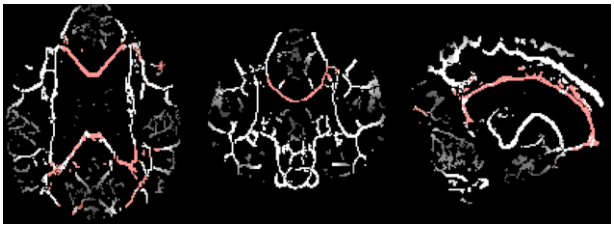

Fig. 2. Results of the voxelwise comparison between AD patients and normal group with TBSS. In red, voxels with $p_{corr}<0.05$ are highlighted.

TABLE I

FA mean (SD)	AD	aMCI	HC	Comparison between groups (p-value)		
				AD-HC	aMCI-AD	aMCI-HC
CC1	0.38 (0.03)	0.41 (0.03)	0.42 (0.02)	0.001	0.02	n.s.
CC2	0.48 (0.04)	0.52 (0.03)	0.54 (0.02)	<0.001	0.01	n.s.
CC3	0.43 (0.03)	0.46 (0.03)	0.48 (0.02)	<0.001	0.01	n.s.
CC4	0.41 (0.03)	0.44 (0.04)	0.47 (0.03)	<0.001	0.04	n.s.
CC5	0.53 (0.04)	0.55 (0.03)	0.57 (0.02)	0.004	n.s.	n.s.
CC6	0.64 (0.03)	0.66 (0.03)	0.67 (0.02)	0.02	n.s.	n.s.
CC7	0.53 (0.05)	0.56 (0.03)	0.58 (0.02)	0.002	n.s.	n.s.

Comparison between mean FA in the 7 CC portions of the three groups of participants, computed with atlas-based tractography. p-values refer to ANOVA test with correction for multiple comparisons, significance level: $p_{corr}<0.05$.