

Corticospinal tract asymmetry and handedness in right- and left-handers by diffusion tensor tractography

Romuald Seizeur, Elsa Magro, Sylvain Prima, Nicolas Wiest-Daesslé, Camille Maumet, Xavier Morandi

► **To cite this version:**

Romuald Seizeur, Elsa Magro, Sylvain Prima, Nicolas Wiest-Daesslé, Camille Maumet, et al.. Corticospinal tract asymmetry and handedness in right- and left-handers by diffusion tensor tractography: Corticospinal tract asymmetry and handedness. *Surgical and Radiologic Anatomy*, Springer Verlag (Germany), 2013, 36 (2), pp.111-124. <10.1007/s00276-013-1156-7>. <inserm-00853861>

HAL Id: inserm-00853861

<https://www.hal.inserm.fr/inserm-00853861>

Submitted on 8 Nov 2013

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 Title: **Corticospinal tract asymmetry and handedness in right- and left-handers by**
2 **diffusion tensor tractography**

3 Running title: **Corticospinal tract asymmetry and handedness**

4

5 Author names and affiliations

6 Romuald Seizeur^{1,2}, Elsa Magro², Sylvain Prima³, Nicolas Wiest-Daesslé³, Camille Maumet³,
7 Xavier Morandi^{4,5}.

8 1. INSERM UMR 1101, LaTIM, Brest, France

9 2. Service de Neurochirurgie, CHRU Cavale Blanche, Brest, France

10 3. IRISA Unité VisAGeS U746 INSERM / INRIA / CNRS /Université. Rennes 1, Rennes,
11 France

12 4. INSERM U 1099, Equipe MediCIS, Rennes, France

13 5. Service de Neurochirurgie, CHU Pontchaillou, Rennes, France

14 Postal address of each affiliation

15 1. LaTIM, INSERM UMR 1101, avenue Foch, Brest, F- 29200 France

16 2. Unité/Projet VisAGeS IRISA, INSERM U 746, Faculté de Médecine, 35043 Rennes
17 Cedex, France

18 3. CHRU Brest, Service de Neurochirurgie, Brest, F- 29200 France

19 4. Equipe MediCIS, INSERM U 1099, Faculté de Médecine, Rennes, F-35043 France

20 5. CHU Pontchaillou, Service de Neurochirurgie, Rennes, F- 35000 France

21

22 Corresponding author: Romuald Seizeur

23 Tel: +33 (0)298347314

24 Fax: +33 (0)298347846

25 E-mail: romuald.seizeur@chu-brest.fr

26 Postal address: Service de Neurochirurgie, Pôle Neurolocomoteur, CHU Cavale Blanche,
27 Boulevard Tanguy Prigent, F- 29200 Brest, France

28

29 “Corticospinal tract asymmetry and handedness in right- and left-handers by diffusion tensor
30 tractography”

31 **Abstract**

32 *Purpose*

33 Cerebral hemispheres represent both structural and functional asymmetry, which differs
34 among right- and left-handers. The left hemisphere is specialized for language and task
35 execution of the right hand in right-handers. We studied the corticospinal tract in right- and
36 left-handers by diffusion tensor imaging and tractography. The present study was aimed at
37 revealing a morphological difference resulting from a region of interest (ROI) obtained by
38 functional MRI (fMRI).

39 *Methods*

40 Twenty-five healthy participants (right-handed: 15, left-handed: 10) were enrolled in our
41 assessment of morphological, functional and diffusion tensor MRI. Assessment of brain fibre
42 reconstruction (tractography) was done using a deterministic algorithm. Fractional anisotropy
43 (FA) and mean diffusivity (MD) were studied on the tractography traces of the reference
44 slices.

45 *Results*

46 We observed a significant difference in number of leftward fibres based on laterality. The
47 significant difference in regard to FA and MD was based on the slices obtained at different
48 levels and the laterality index. We found left hand asymmetry and right hand asymmetry
49 respectively for the MD and FA.

50 *Conclusions*

51 Our study showed the presence of hemispheric asymmetry based on laterality index in right-
52 and left-handers. These results are inconsistent with some studies and consistent with
53 others. The reported difference in hemispheric asymmetry could be related to dexterity
54 (manual skill).

55 *Keywords:* corticospinal tract, deterministic tractography, diffusion tensor imaging, anatomy,
56 MRI.

57

59 Introduction

60 Cerebral hemispheric asymmetry was brought up by Hippocrates. He demonstrated how a
61 head wound on one side led to seizures and a hemiplegia of the opposite side of the body (*in*
62 Adams [1]). Since antiquity, many descriptions of brain hemispheric asymmetry have been
63 given. These regard the gray matter (cerebral cortex [29] and the basal ganglia [35]), as well
64 as the white matter [27, 53].

65 Handedness is one example of lateralization of cerebral functions [15]. Several studies have
66 shown a difference in hemispheric asymmetry, between right- and left-handers [27, 28],
67 according to the assessed functions. Left hemisphere is attributed to language, gnosis and
68 praxia. Right hemisphere is attributed to visuospatial and visuoconstructive perceptions and
69 attention [20]. Language lateralization related to handedness was described by Broca in
70 1863 [8], stating that left hemisphere was specialized for language and the dominant hand
71 manual task. Geschwind et al. [20, 21] showed that the left *planum temporale* was wider than
72 the right one. Thus, these authors put forward an association between brain anatomical
73 asymmetry and handedness.

74 More recently, in vivo magnetic resonance imaging (MRI) assessment of encephalic volume
75 revealed the gray and white matter asymmetries [22, 39]. These studies were consistent with
76 previous ones revealing a morphological lateralization of different cerebral lobes. Kertesz et
77 al. [28] showed such lateralization by comparing 52 right-handers with 52 left-handers. They
78 put forward an association between left hemispheric dominance and wider right frontal and
79 left occipital lobes. Other studies have found an association between the depth of central
80 sulcus and handedness [3], or a lateralization of lateral sulcus based on *planum temporale*
81 asymmetry [42]. The encephalon MRI morphometry assessment of central sulcus by Amunts
82 et al. [3] in 31 right-handed and 14 left-handed men, revealed a leftward lateralization of
83 central sulcus in the right-handers. The left-handers showed a less significant lateralization.
84 These authors assumed an association between handedness and a wider cerebral cortex
85 area and likely a more significant cerebral connectivity. In a more recent study [2] by Amunts
86 et al., the leftward lateralization of central sulcus was only observed in men. As a result, a
87 difference in organisation of the cortex related to hand mobility between men and women
88 was reported. Rubens et al. [42] evaluated 36 bodies by cerebral hemisphere photographic
89 methods and assessing the length and shape of the lateral sulcus. The left lateral
90 hemisphere was reported to be longer and more rectilinear than the right one. This could
91 affect the size of neighboring brain structures such as *planum temporale*. The results of an
92 evaluation of 100 bodies by Geschwind and Levitsky [21], were consistent with those of
93 Rubens et al.: in accordance to the length of lateral sulcus, the left *planum temporale* was

94 reported to be wider (65% of cases) than the right one. However, Saenger et al. [43] studied
95 brain asymmetries using MRI functional connectivity and gray matter volume in right- and
96 left-handers. They concluded that functional asymmetries are not always concordant with
97 morphological asymmetries.

98 Some authors also studied the association between handedness, or possible existence of
99 dexterity (manual skill), and lateralization of the white matter [9, 24, 52]. Today, diffusion
100 tensor imaging (DTI) and tractography allow the reconstruction of fibre tracts and even
101 bringing light into the possible association between lateralization of the corticospinal tract
102 (CST) and handedness. Büchel et al. [9] showed an increase in fractional anisotropy (FA)
103 within the precentral gyrus, contralateral to the dominant hand. They revealed the following:
104 an association between cerebral asymmetry and handedness, and the role of DTI in the
105 assessment of the white matter. Westerhausen et al. [52] DTI assessment of the association
106 between cerebral asymmetry and internal capsule asymmetry was conclusive. However, no
107 evident correlation between internal capsule asymmetry and laterality was revealed. In his
108 2002 literature review, Hammond [24] stated that the dominant hemisphere, contralateral to
109 the dominant hand, represented a better functional organisation via an increase in cortical
110 connectivity of the primary motor area (M1). This could explain the better manual task
111 performance of the dominant hand but does not prove a correlation with the CST volume.

112 The aim of our study was to evaluate the correlation between handedness and cerebral
113 asymmetry through focusing on hand motor fibres within the CST. Using deterministic
114 tractography, we aimed to highlight a difference between the right- and left- handers. The
115 choice of our method followed the footsteps of a previous study [44] by comparing the
116 following parameters: FA and mean diffusivity (MD).

117

118 **Material**

119

120 *Subjects*

121 Twenty-five healthy volunteers were enrolled in this study: fifteen right-handers (ten men and
122 five women) and ten left-handers (six men and four women). They had no history of
123 neurological disorders. Age ranged from 22 years to 46 years (mean age 30.8 years) for
124 right-handers and 18 years to 42 years (mean age 29.2) for left-handers. Written informed
125 consent was obtained from each subject and data were handled anonymously. Handedness

126 was determined using a test created by Dellatolas [17] for use on the healthy population in
127 France, adapted from studies by Annett [4] and Oldfield [34]. Index laterality is summarised
128 in table 1.

129

130 *Magnetic Resonance (MR) data acquisition*

131

132 Brain MR scans were carried out on each volunteer. MRI scans were performed on a Philips
133 Achieva 3T system (Philips Medical Systems, Best, The Netherlands) using an 8-channel
134 head coil. All volunteers were in supine position. To minimise involuntary head motion,
135 bitemporal maintenance points were used.

136

137 The protocol used was the following:

138 - *Morphological MRI*: T1-weighted sequence in single shot echo-planar. All acquired volumes
139 contained 184 sagittal slices, field of view (FOV): 256x256 mm; acquisition matrix: 256 x 256;
140 voxel size: 1 x 1 x 1 mm³; TE / TR / Flip angle: 4.6 ms / 9.9 ms / 8°; SENSE factor: 2. Total
141 duration of this sequence was 3min53s.

142

143 - *Functional imaging sequence*

144 The fMRI acquisition sequence used gradient echo-planar imaging (EPI) to provide BOLD
145 contrast (blood oxygen-level dependent). Each volume represented comprised 24 contiguous
146 4 mm axial slices parallel to the AC-PC line, with parameters as follows: FOV: 230 mm;
147 acquisition matrix: 80 x 80; reconstruction matrix after interpolation: 128 x 128; reconstructed
148 voxel size: 1.8 x 1.8 x 4 mm³; TE / TR / Flip angle: 35 ms / 3000 ms / 90°. The acquisition of
149 this 24-slice volume was repeated 62 times. Total duration of each sequence was 3min12s.

150 The paradigm followed a block design: seven interleaved 30s phases of rest and motor tasks
151 were recorded. The motor tasks consisted of opening and closing the hand. After a period to
152 obtain gradient stabilisation, acquisition of the first two 24-slice volumes was performed (6 s)
153 in three sequences of alternating rest and activation, beginning with rest.

154 This protocol was performed twice, once for the right hand and once for the left one.

155

156 - *Diffusion weighted imaging (DWI) sequence*

157 The DWI acquisition sequence was an EPI, single shot spin echo Stejskal Tanner sequence,
158 combined with SENSE parallel imaging. Diffusion gradients were applied in 15 noncollinear
159 directions with $b = 800 \text{ sec/mm}^2$. Parameters were as follows: 60 2-mm slices; FOV: 256 mm;
160 acquisition matrix and reconstructed matrix: 128 x 128; reconstructed voxel size: 2 x 2 x 2
161 mm^3 ; TE / TR / Flip angle: 64 ms / 10000 ms / 90°; SENSE factor: 3. Total duration of this
162 sequence was 6min.12s.

163

164 **Method**

165

166 *Data processing and post-processing*

167

168 *Morphological MRI*

169 The MRI T1-weighted sequence was used to obtain a morphological image. This image was
170 used to segment ROIs and to visualize fibre bundles and ROIs on the same image after
171 registration of all sequences.

172 This sequence was used to determinate axial reference slices using fixed landmarks for all
173 subjects. Three reference slices (Figure 1) were localised in corona radiate, internal capsule
174 and diencephalon-mesencephalon junction. Diffusion parameters were recorded on these
175 slices.

176

177

178 *Functional MRI*

179 All post-processing calculations were carried out using SPM5 routines (statistical
180 parametrical mapping SPM5 / Wellcome Department of Neurology, Institute of Neurology,
181 London) as well as in-house Matlab scripts (Matlab (2007), The MathWorks Inc). The 24-
182 slice, 62 volumes were automatically realigned with the first to correct head motions. For
183 each volunteer, all volumes were smoothed (smoothness window: 6x6x6). Individual
184 statistical parametric maps were calculated using the general linear model [19] to compare
185 brain activation and stimulation. At the first level, the design matrix included one regressor to
186 model the block paradigm with implicit baseline ("1" for action scans, "0" for rest scans). For
187 each paradigm (left/right), the effect of interest was evaluated with the following contrast:
188 $c=1$. Anatomical data and fMRI data were normalised and coregistered (nonlinear
189 registration). Coregistered volumes were visually inspected to assess the quality of the
190 registration. The fMRI data were used to segment a part of the superior ROI.

191

192 *DTI data*

193 Diffusion weighted imaging (DWI) scans were first realigned and corrected for eddy currents
194 distortions. Each DWI image was realigned with the non-weighted image ($b=0$ s/mm²). For
195 each voxel, a tensor was estimated using a linear regression method [18]. Tensor being a
196 3x3 symmetric definite positive matrix, it was diagonalised to obtain its eigenvalues (strictly
197 positives) for each voxel, from which fractional anisotropy (FA) and mean diffusivity (MD)
198 maps were derived.

199

200 *Fibre tracking*

201 DTI fibre tracking was performed using in-house software implementation of conventional
202 fibre tracking algorithms. A deterministic algorithm was used. It was an integration method
203 derived from the fibre assignment by continuous tracking (FACT) method [32], using second-
204 order Runge-Kutta (RK2) [6, 14].

205 Integration methods use constant integration step size. The FACT method allows the
206 prediction of the position of different points all along the fibre curve. The direction was
207 provided step by step; the step size was 1mm (voxel size). The RK2 method provided an
208 estimation of the trajectory. This trajectory was used to estimate a second, more precise
209 trajectory using one other estimation of this trajectory.

210

211 *ROI segmentation*

212 We chose to track the CST with a multiple ROI method: the superior ROI (cortical area); the
213 inferior ROI (in the mesencephalon); and an exclusion ROI in the median sagittal plane. The
214 ROIs were segmented by a neuroanatomist.

215 The superior ROI was segmented using motor activation (fMRI) and the T1-weighted MR
216 images. Since this study focused on the CST, all non-cortical activations (e.g. cerebellar)
217 were discarded. We retain the activation from the fMRI corresponding to the hand motor area
218 using the anatomical landmark of the precentral gyrus described by Yousry et al. [54], and its
219 variations [11]. To focus the superior ROI around the hand motor area, a segmentation
220 algorithm (all non-connected components were discarded) was used to suppress adjacent
221 activations, i.e. contralateral activation, venous artefacts, activations from supplementary
222 motor area. This method allowed the preservation of each subject's motor activation in the
223 motor area [31] (Figure 2).

224 The inferior ROI was determined by manual segmentation based on our knowledge of the
225 CST anatomy in the mesencephalon. This ROI was located in the anterior part of the
226 peduncle (*crus cerebri*) (Figure 2). This segmentation was performed on the T1-weighted MR
227 image with Anatomist software (BrainVISA/Anatomist version 3.0.2).

228 A third ROI was considered and represented by the median sagittal plane. The fibre
229 reconstruction was done step by step hence this third ROI could not be reached by the
230 fibres.

231 *CST reconstruction by fibre tracking*

232 CST was reconstructed (tractography), using the algorithm based on RK2 previously
233 described, and between ROIs (superior and inferior). The fibres could not go through the
234 sagittal median plane (Figure 2). Two parameters were fixed to stop the tracking: the minimal
235 FA value was set to 0.2 and the maximal angle between two adjacent eigenvectors
236 (deviation angle) was less than 45°.

237 At each axial, coronal and sagittal slice, we observed and saved the fibre passing points. The
238 latter were called "traces". Traces were studied on the reference slice, described before, with
239 the point by point mean measurement of FA and MD (Figure 3).

240

241 *Evaluation*

242 Each fibre bundle was visually verified to ensure the quality and the reliability of the images.
243 Asymmetry and laterality were evaluated by several measurements: superior ROI volumes,
244 fibre number for all subjects on both sides, FA and MD on reference slices

245

246 *Statistical analysis*

247 For statistical analysis, Student t-tests were used for quantitative results (i.e. fibre number
248 and superior ROI volume) and a *Spearman correlation test* was used to find a correlation
249 between laterality and the measured parameters (FA, MD).

250 All statistical analyses were conducted using the SAS software (SAS Institute Inc., version
251 9.2).

252

253 **Results**

254 *ROI volume and laterality*

255 The ROI volumes are displayed in Table 2. No significant difference was observed between
256 left and right regions in right- and left-handers ($p=0.83$). No significant difference was
257 observed between right ($p=0.29$), and left ($p=0.07$) based on laterality.

258

259 *Fibre numbers and laterality*

260 The results of number of fibres are displayed in Table 3. No significant difference was
261 observed for the right hand side (*r*) or the left hand side (*l*), in right- ($p=0.31$) and left-
262 handers ($p=0.12$). However, a significant difference based on laterality was reported for the
263 left hand side ($p=0.03$) and none for the right hand side ($p=0.18$).

264

265

266

267

268 *Fractional anisotropy and laterality*

269 The FA measurements by level, side (r or l) and laterality (R or L) are summarised in Figure
270 4. Table 4 displays handedness and laterality results, the FA measurements: the minimum,
271 the maximum, the means, the medians and the p values.

272 In regard to asymmetry, we observed a significant difference in the right-handers at 2 of the 3
273 levels of the slice (level 2: $p < 0.0001$ and level 3: $p < 0.0001$). In fact, the FA mean and median
274 of the above 2 levels were higher for the left hand side. However, in the left-handers, level 2
275 ($p = 0.0007$) and 3 ($p = 0.0001$) means were higher for the right hand side.

276 In regard to laterality, very significant differences were observed at the 3 levels of the slice:
277 FA measurement was higher for the right-handers (both sides). The exception to this was
278 reported for the left hand side at level 1 where *corona radiata* was not significantly different.

279

280 *Mean diffusivity and laterality*

281 Figure 5 displays all the MD measurements: by level, side (r or l), and laterality (R or L).
282 Table 5 displays the MD results: minimum and maximum, means, medians and p values.

283 In regard to asymmetry, a significant difference was observed at slice level 2 ($p < 0.0001$) in
284 the right-handers. The mean and median were higher for the right hand side. There was a
285 significant difference at the 3 slice levels in the left-handers: level 1, 2 and 3, p -values were
286 respectively 0.0111, < 0.0001 , and < 0.0001 . The means were reported to be higher for the
287 right hand side.

288 In regard to laterality, significant differences were reported at the 3 slice levels. At the slice
289 level 1 and 2 for the left hand side and level 3 for the right hand side (all 3 levels of slice
290 $p < 0.0001$).

291

292 *Laterality correlation with FA and MD*

293 A correlation was reported for the FA ($r= 0.107$; $p<0.0001$) and MD ($r=-0.051$; $p=0.0199$)
294 based on laterality in the left-handers (Table 1).

295

296

297 **Discussion**

298 Our results highlighted significant differences of FA and MD parameters at three different
299 slice levels. In addition, we revealed a correlation between the laterality index and the FA
300 and MD parameters. We would like to emphasize that in this study, the fMRI images labeled
301 “right” or “left” side refers to the “hand” that was used for motor function assessment, i.e. the
302 right hand side referred to the left hemisphere. Indeed, most of the literature mentioned here
303 reported the cerebral hemisphere on which their study was based.

304 We selected one of the three ROI that was segmented from functional data taking into
305 account the motor function area of the hand [30]. This study did not show a significant
306 difference either of hemispheric asymmetry or laterality association with the ROI volumes.
307 These results are not consistent with those of the literature reporting asymmetry of the motor
308 functions by fMRI. This could be a bias of our results, given the published evidence that the
309 functional activation is more important at the left motor cortex in right-handers (for the
310 mobility of right and left hand) [23, 29]. This could be explained by the several CST fibres
311 which do not decussate [53]. Other explanation could be the association with the laterality
312 index. Dassonville et al. [16] studied the fMRI motor function of the dominant and non-
313 dominant hand in seven right-handers and six left-handers. They demonstrated that the
314 cortical function is more important for the dominant hand and that it is correlated with the
315 laterality index in both right- and left-handers.

316 The hemispheric asymmetry revealed in our study was that of the left hand side FA, and that
317 of the right hand side MD (i.e. respectively, the right and left hemisphere). In regard to the
318 FA, we reported a significant difference between the right- and left-handers with a larger FA
319 at right and left in the right-handers. The FA increased based on the laterality index in left-
320 handers (7 to 20/20). There was no evidence of such correlation in the right-handers since
321 our sample consisted of real right-handers except for one slightly ambidextrous (1/20). The
322 FA points out the diffusion process direction [7] and it is influenced by axon myelination,
323 cellular density as well as fibre diameter [46]. Our results are not consistent with those of the
324 reviewed literature and did not conclude a difference in fibre organisation between the right-

325 and left-handers. Sullivan et al. [49], in their study on internal capsule FA in 24 right-handers,
326 found different FA measures in different zones. They stated that this variation of FA was
327 related to the diversity of fibres passing through the internal capsule. Our study took into
328 account an overall FA at each slice level, but by analysing the fibres resulting from RK2
329 algorithm of CST reconstruction. We would like to emphasize the limitation of our fibres
330 reconstruction method, deterministic tractography, unable to resolve “crossing” and “kissing”
331 fibre bundles within a voxel [12, 40]. Our MD results were similar to the FA ones. However,
332 there was a significant difference at the three slice levels: less homogenous results in regard
333 to only one side at each level. A difference was reported at two slice levels for the left hand
334 side, (i.e. the right hemisphere), being the non-dominant hand in right-handers and less often
335 dominant in left-handers (15% of the cases [38]).

336 Our DTI and tractography study, at several levels of encephalon, of the white matter tracts
337 run by CST hand motor fibres, did not allow to show a clear significant difference between
338 the right- and left-handers. Several authors [9, 36, 41, 50, 52] have demonstrated an
339 asymmetry between the right and left side of the encephalon. Some authors [41, 50], have
340 reported results consistent with ours in regard to FA. Toosy et al. [50], in their study of 21
341 cases with amyotrophic lateral sclerosis and 14 controls, showed a gradual decrease of FA
342 on the rostro-caudal axis in the controls. The FA was reported to have more significant
343 difference at the internal capsule of the right hemisphere. The FA decrease was explained by
344 the size of the studied structure within the brainstem and the number of crossing fibres. The
345 above results cannot be compared with ours since we did not study the brainstem. Reich et
346 al. [41], in their 3T scan assessment of CST in 20 volunteers, obtained a correlation between
347 inter-hemispheric number of fibres. This asymmetry varies based on the zone in the nervous
348 system, and an increase in MD asymmetry has been shown in the assessment of
349 hemispheric zone of right CST. This was demonstrated in the study of posterior limb of
350 internal capsule of 60 volunteers (30 right-handers and 30 left-handers) by Westerhausen et
351 al. [52]. These authors showed an increase in left-hand FA and right-hand MD. However, no
352 difference was observed based on laterality. One possible explanation was that the dominant
353 hand muscles to be more innervated than the non-dominant hand muscles. This could
354 explain the dexterity hypothesis [24].

355 To date, Büchel et al. [9] are the only authors demonstrating an association between
356 handedness and part of the encephalon through an assessment of their second group (28
357 cases). They found asymmetric FA in the precentral gyrus, contralateral to the dominant
358 hand. In their MRI morphometric evaluation of 56 young right-handed men, Hervé et al. [26]
359 revealed asymmetric gray matter in the precentral and central regions and no neighbouring

360 white matter difference despite the observed left hand side asymmetry. In their fMRI DTI
361 study of arcuate fasciculus in 12 cases (seven right-handers), Vernooij et al. [51] used CST
362 as the reference bundle. They reported leftward asymmetric arcuate fasciculus without any
363 relation with laterality (dominant hand or language), consistent with a previous study on CST
364 (Cicarelli et al. [13]) and contrary to others on motor system [2, 3, 26].

365 Decussation of CST fibres could be one explanation for not observing an evidence of
366 correlation with laterality. Yakovlev et Rakic [53], in their dissection of fibre bundles in 100
367 medulla oblonga and 130 spinal cords of foetus and new-borns, demonstrated that in 2/3 of
368 the cases, there were more left hemisphere fibres decussating to the right, and more right
369 hemisphere fibres running to the right of spinal cord. Consequently, the right side of the
370 spinal cord could be considered as the dominant side since it receives more fibres from both
371 sides of the encephalon. Thereafter, Kertesz et Geschwind [27] conducted a similar study by
372 taking into account handedness of the cases, but did not find a correlation with laterality.
373 Consistent results of a more recent study [33] on 70 spinal cord cases revealed right side
374 fibre asymmetry in $\frac{3}{4}$ of the cases, and more fibres running to the right than left in $\frac{3}{4}$ of the
375 cases. However, there was no evidence of correlation with handedness, sole a correlation
376 with dexterity was suspected.

377 Laterality is different between men and women. There are more right-handed women, and
378 thus more (> 25%) non-right-handed men (ambidextrous and left-handers) [47]. Hervé et al.
379 [26] described a less significant *planum temporale* asymmetry in left-handers men.
380 Shapleske et al. [45] found a significant *planum temporale* asymmetry for the left hand side.
381 This difference was reported to decrease in left-handers and women. Amunts et al. [2] found
382 that central sulcus was deeper based on laterality only in men (right central sulcus was
383 deeper in 62% of left-handers). Pujol et al. [39] reported hemispheric volume asymmetry on
384 MRI revealing a larger left hemisphere. This hemispheric volume asymmetry was reported to
385 be more significant in men. Powell et al. [37] performed voxel-based statistical analysis on
386 FA maps of 42 right-handers and 40 left handers. Leftward anisotropy was found in arcuate
387 fasciculus regions (greater in right-handers). Studying differences between men and women,
388 they concluded that sex had greater effect than handedness on FA asymmetries. In the
389 previous cited study by Westerhausen et al. [52], a significant difference was reported with
390 an increase in FA in male brains. These authors suggested a difference in CST organisation
391 and structure within internal capsule between men and women. Given the bigger size of
392 men's brain, the above hypothesis may indicate a variation of CST and thus of parameters
393 such as FA representing its structure. The gender volume asymmetry difference disappeared

394 after matching data for brain size. Catani et al. [10] studied 40 right-handed adults and
395 reported no difference in CST volume and FA parameter between men and women.

396 Most of the literature aiming at determining an association between asymmetry and laterality
397 used a small sample size leading to their results limitation [25]. In addition, it is well known
398 that left-handers are not a homogenous population – their dominant hemisphere is the right
399 hemisphere in 15% of the cases [38] while some could be culturally and environmentally
400 forced into right-handedness. In fact, most of variation in handedness is due to genetic
401 effects [5], the rest being attributable to environmental influences [15]. Assessment of
402 laterality is often done by various methods. It is worth mentioning that some studies have not
403 used any assessment method [25]. For instance, Good et al. [22], conducted their laterality
404 assessment of 67 left- and 398 right-handers based on the dominant hand for writing. Such
405 assessment has its limitation in regard to the impact of laterality [47]. We chose an
406 assessment method derived from studies done on a sample of French population free of
407 neurological pathologies (e.g. our sample) [17].

408

409 To conclude, consistent with other studies, we demonstrated a CST hand motor task
410 asymmetry in relation with laterality. In line with the literature [10], our study had its
411 limitations such as our deterministic tractography method and our small size for each group.
412 Our results did not allow us to draw conclusions in terms of laterality index. Thus, we suggest
413 larger scale studies using other assessment methods such as diffusion direction imaging
414 [48], i.e. MRI with a low angle diffusion, to obtain a more precise CST reconstruction in
415 particular in the crossing and kissing fibre zones.

416

417 **Acknowledgements**

418 The authors would like to warmly thank Zarrin Alavi (MSc), INSERM CIC 0502, for her
419 assistance to realize this manuscript.

420

421 **Conflict of interest**

422 The authors declare no conflict of interest in the realization of this study.

423

424 References

425

- 426 1. Adams F (1849) The genuine works of Hippocrates. William Woods, New York.
- 427 2. Amunts K, Jancke L, Mohlberg H, Steinmetz H, Zilles K (2000) Interhemispheric
428 asymmetry of the human motor cortex related to handedness and gender.
429 *Neuropsychologia* 38:304-312
- 430 3. Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K
431 (1996) Asymmetry in the human motor cortex and handedness. *Neuroimage* 4:216-222
- 432 4. Annett M (1970) A classification of hand preference by association analysis. *Br J Psychol*
433 61:303-321
- 434 5. Annett M (1998) Handedness and cerebral dominance: the right shift theory. *J*
435 *Neuropsychiatry Clin Neurosci* 10:459-469
- 436 6. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A (2000) In vivo fiber tractography
437 using DT-MRI data. *Magn Reson Med* 44:625-632
- 438 7. Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system - a
439 technical review. *NMR Biomed* 15:435-455
- 440 8. Broca P (1863) Localisation des fonctions cérébrales. Siège du langage articulé. *Bull Soc*
441 *Anthropol* 4:200-204
- 442 9. Büchel C, Raedler T, Sommer M, Sach M, Weiller C, Koch MA (2004) White matter
443 asymmetry in the human brain: a diffusion tensor MRI study. *Cereb Cortex* 14:945-951
- 444 10. Catani M, Forkel S, Thiebaut de SM (2010) Asymetry of white matter pathways. 177-209
- 445 11. Caulo M, Briganti C, Mattei PA, Perfetti B, Ferretti A, Romani GL, Tartaro A, Colosimo C
446 (2007) New morphologic variants of the hand motor cortex as seen with MR imaging in a
447 large study population. *AJNR Am J Neuroradiol* 28:1480-1485
- 448 12. Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A (2008) Diffusion-based
449 tractography in neurological disorders: concepts, applications, and future developments.
450 *Lancet Neurol* 7:715-727
- 451 13. Ciccarelli O, Parker GJ, Toosy AT, Wheeler-Kingshott CA, Barker GJ, Boulby PA, Miller
452 DH, Thompson AJ (2003) From diffusion tractography to quantitative white matter tract
453 measures: a reproducibility study. *Neuroimage* 18:348-359
- 454 14. Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton
455 H, Raichle ME (1999) Tracking neuronal fiber pathways in the living human brain. *Proc*
456 *Natl Acad Sci U S A* 96:10422-10427

- 457 15. Corballis MC, Badzakova-Trajkov G, Häberling IS (2012) Right hand, left brain: genetic
458 and evolutionary bases of cerebral asymmetries for language and manual action. *WIREs*
459 *Cogn Sci* 3:1-17
- 460 16. Dassonville P, Zhu XO, Ugurbil K, Kim SG, Ashe J (1997) Functional activation in motor
461 cortex reflects the direction and the degree of handedness. *Proc Natl Acad Sci U S A*
462 94:14015-14018
- 463 17. Dellatolas G, De Agostini M, Jallon P, Poncet M, Rey M, Lellouch J (1988) Mesure de la
464 préférence manuelle par autoquestionnaire dans la population française adulte. *Revue de*
465 *Psychologie appliquée* 38:117-136
- 466 18. Fillard P, Arsigny V, Pennec X, Hayashi KM, Thompson PM, Ayache N (2007) Measuring
467 brain variability by extrapolating sparse tensor fields measured on sulcal lines.
468 *Neuroimage* 34:639-650
- 469 19. Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RS (1995)
470 Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain*
471 *Mapp* 2:189-210
- 472 20. Geschwind N (1972) Cerebral dominance and anatomic asymmetry. *N Engl J Med*
473 287:194-195
- 474 21. Geschwind N, Levitsky W (1968) Human brain: left-right asymmetries in temporal speech
475 region. *Science* 161:186-187
- 476 22. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001)
477 Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-
478 based morphometric analysis of 465 normal adult human brains. *Neuroimage* 14:685-700
- 479 23. Gut M, Urbanik A, Forsberg L, Binder M, Rymarczyk K, Sobiecka B, Kozub J, Grabowska
480 A (2007) Brain correlates of right-handedness. *Acta Neurobiol Exp (Wars)* 67:43-51
- 481 24. Hammond G (2002) Correlates of human handedness in primary motor cortex: a review
482 and hypothesis. *Neurosci Biobehav Rev* 26:285-292
- 483 25. Hatta T (2007) Handedness and the brain: a review of brain-imaging techniques. *Magn*
484 *Reson Med Sci* 6:99-112
- 485 26. Hervé PY, Crivello F, Perchey G, Mazoyer B, Tzourio-Mazoyer N (2006) Handedness
486 and cerebral anatomical asymmetries in young adult males. *Neuroimage* 29:1066-1079
- 487 27. Kertesz A, Geschwind N (1971) Patterns of pyramidal decussation and their relationship
488 to handedness. *Arch Neurol* 24:326-332
- 489 28. Kertesz A, Polk M, Black SE, Howell J (1992) Anatomical asymmetries and functional
490 laterality. *Brain* 115 (Pt 2):589-605
- 491 29. Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP
492 (1993) Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry
493 and handedness. *Science* 261:615-617

- 494 30. Kim YH, Kim DS, Hong JH, Park CH, Hua N, Bickart KC, Byun WM, Jang SH (2008)
495 Corticospinal tract location in internal capsule of human brain: diffusion tensor
496 tractography and functional MRI study. *Neuroreport* 19:817-820
- 497 31. Lotze M, Erb M, Flor H, Huelsmann E, Godde B, Grodd W (2000) fMRI evaluation of
498 somatotopic representation in human primary motor cortex. *Neuroimage* 11:473-481
- 499 32. Mori S, Crain BJ, Chacko VP, van Zijl PC (1999) Three-dimensional tracking of axonal
500 projections in the brain by magnetic resonance imaging. *Ann Neurol* 45:265-269
- 501 33. Nathan PW, Smith MC, Deacon P (1990) The corticospinal tracts in man. Course and
502 location of fibres at different segmental levels. *Brain* 113 (Pt 2):303-324
- 503 34. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh
504 inventory. *Neuropsychologia* 9:97-113
- 505 35. Peterson BS, Riddle MA, Cohen DJ, Katz LD, Smith JC, Leckman JF (1993) Human
506 basal ganglia volume asymmetries on magnetic resonance images. *Magn Reson Imaging*
507 11:493-498
- 508 36. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA,
509 Barker GJ, Noppeney U, Koepp MJ, Duncan JS (2006) Hemispheric asymmetries in
510 language-related pathways: a combined functional MRI and tractography study.
511 *Neuroimage* 32:388-399
- 512 37. Powell JL, Parkes L, Kemp GJ, Sluming V, Barrick TR, Garcia-Finana M (2012) The
513 effect of sex and handedness on white matter anisotropy: a diffusion tensor magnetic
514 resonance imaging study. *Neuroscience* 207:227-242
- 515 38. Pujol J, Deus J, Losilla JM, Capdevila A (1999) Cerebral lateralization of language in
516 normal left-handed people studied by functional MRI. *Neurology* 52:1038-1043
- 517 39. Pujol J, Lopez-Sala A, Deus J, Cardoner N, Sebastian-Galles N, Conesa G, Capdevila A
518 (2002) The lateral asymmetry of the human brain studied by volumetric magnetic
519 resonance imaging. *Neuroimage* 17:670-679
- 520 40. Qazi AA, Radmanesh A, O'Donnell L, Kindlmann G, Peled S, Whalen S, Westin CF,
521 Golby AJ (2009) Resolving crossings in the corticospinal tract by two-tensor streamline
522 tractography: Method and clinical assessment using fMRI. *Neuroimage* 47 Suppl 2:T98-
523 106
- 524 41. Reich DS, Smith SA, Jones CK, Zackowski KM, van Zijl PC, Calabresi PA, Mori S (2006)
525 Quantitative characterization of the corticospinal tract at 3T. *AJNR Am J Neuroradiol*
526 27:2168-2178
- 527 42. Rubens AB, Mahowald MW, Hutton JT (1976) Asymmetry of the lateral (sylvian) fissures
528 in man. *Neurology* 26:620-624

- 529 43. Saenger VM, Fernando FA, Martinez-Gudino ML, Alcauter S (2012) Hemispheric
530 asymmetries of functional connectivity and grey matter volume in the default mode
531 network. *Neuropsychologia* 50:1308-1315
- 532 44. Seizeur R, Wiest-Daessle N, Prima S, Maumet C, Ferre JC, Morandi X (2012)
533 Corticospinal tractography with morphological, functional and diffusion tensor MRI: a
534 comparative study of four deterministic algorithms used in clinical routine. *Surg Radiol*
535 *Anat* 34:709-719
- 536 45. Shapleske J, Rossell SL, Woodruff PW, David AS (1999) The planum temporale: a
537 systematic, quantitative review of its structural, functional and clinical significance. *Brain*
538 *Res Brain Res Rev* 29:26-49
- 539 46. Shimony JS, McKinstry RC, Akbudak E, Aronovitz JA, Snyder AZ, Lori NF, Cull TS,
540 Conturo TE (1999) Quantitative diffusion-tensor anisotropy brain MR imaging: normative
541 human data and anatomic analysis. *Radiology* 212:770-784
- 542 47. Sommer IEC (2010) Sex differences in handedness, brain asymmetry, and language
543 lateralization. *Information Processing in the Cerebral Hemispheres*. 277-312
- 544 48. Stamm A, Perez P, Barillot C (2011) Diffusion Directions Imaging (DDI). Technical report,
545 INRIA
- 546 49. Sullivan EV, Zahr NM, Rohlfing T, Pfefferbaum A (2010) Fiber tracking functionally
547 distinct components of the internal capsule. *Neuropsychologia* 48:4155-4163
- 548 50. Toosy AT, Werring DJ, Orrell RW, Howard RS, King MD, Barker GJ, Miller DH,
549 Thompson AJ (2003) Diffusion tensor imaging detects corticospinal tract involvement at
550 multiple levels in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 74:1250-
551 1257
- 552 51. Vernooij MW, Smits M, Wielopolski PA, Houston GC, Krestin GP, van der LA (2007)
553 Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric
554 language lateralization in both right- and left-handed healthy subjects: a combined fMRI
555 and DTI study. *Neuroimage* 35:1064-1076
- 556 52. Westerhausen R, Huster RJ, Kreuder F, Wittling W, Schweiger E (2007) Corticospinal
557 tract asymmetries at the level of the internal capsule: is there an association with
558 handedness? *Neuroimage* 37:379-386
- 559 53. Yakovlev P, Rakic P (1966) Patterns of decussation of bulbar pyramids and distribution of
560 pyramidal tracts on two sides of spinal cord. *Trans Am Neurol Assoc* 81:366-367
- 561 54. Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997)
562 Localization of the motor hand area to a knob on the precentral gyrus. A new landmark.
563 *Brain* 120 (Pt 1):141-157
- 564

565

566

567

568 Figures

569 Fig 1 Coronal slice of the brain through the anterior commissure. Reference slices in the brain for the study of traces. Level 1
570 (*corona radiata*), dorsal part of corpus callosum. Level 2 (internal capsule), dorsal part of the lenticular nucleus. Level 3
571 (diencephalon-mesencephalon junction), ventral part of the lenticular nucleus.

572

573 Fig 2 Coronal slice: tractography visualisation from merged images. Morphological MRI (T1); superior ROI (A and A'); inferior
574 ROI (B); sagittal median plan (C); tractographies (blue and red colours, right- and left- hand fibres respectively). Axial slice: crus
575 cerebri, inferior ROI on left side, location of CST on right side.

576

577 Fig 3 Tractography traces. Top left: coronal slice, top right: sagittal slice. Bottom: left to right, slice level inferior (1), middle (2),
578 superior (3). In white colour we visualised all points representing the traces with a clear asymmetry in the present case.

579

580 Fig 4: The FA measurements by level (lev), side (r or l) and laterality (R or L), along with the best fitted linear regression plot

581 (a) In Right-handers (R), (b) In Left-handers (L)

582

583 Fig 5: The MD measurements by level (lev), side (r or l) and laterality (R or L), along with the best fitted linear regression plot

584 (a) In Right-handers (R), (b) In Left-handers (L)

585

586 Tables

587

588 Table 1

589 Score and Laterality of subjects, test from [17], ranged from 0 to 20. R: right-hander (0/20), RA: right-handed ambidextrous (1 to
590 6/20), L: left-hander (17 to 20/20), LA: left-handed ambidextrous (7 to 16/20).

591

592 Table 2

593 Quantitative results, ROI volumes (mm³) from both right (r) and left (l) hand fMRI. Right-handers (R) are ranked 1 to 15, left-
594 handers (L) are ranked 16 to 25. SD: Standard Deviation.

595

596 Table 3

597 Quantitative results, number of fibres for RK2 algorithm. Right-handers (R) are ranked 1 to 15, left-handers (L) are ranked 16 to
598 25. SD: Standard Deviation.

599

600 Table 4

601 Brain asymmetry from laterality, FA results, mean, median, Standard Deviation (SD) and p value (t test). R vs L (right-side):
602 looking for a significant difference between right-handers (R) and left-handers (L) based on laterality.

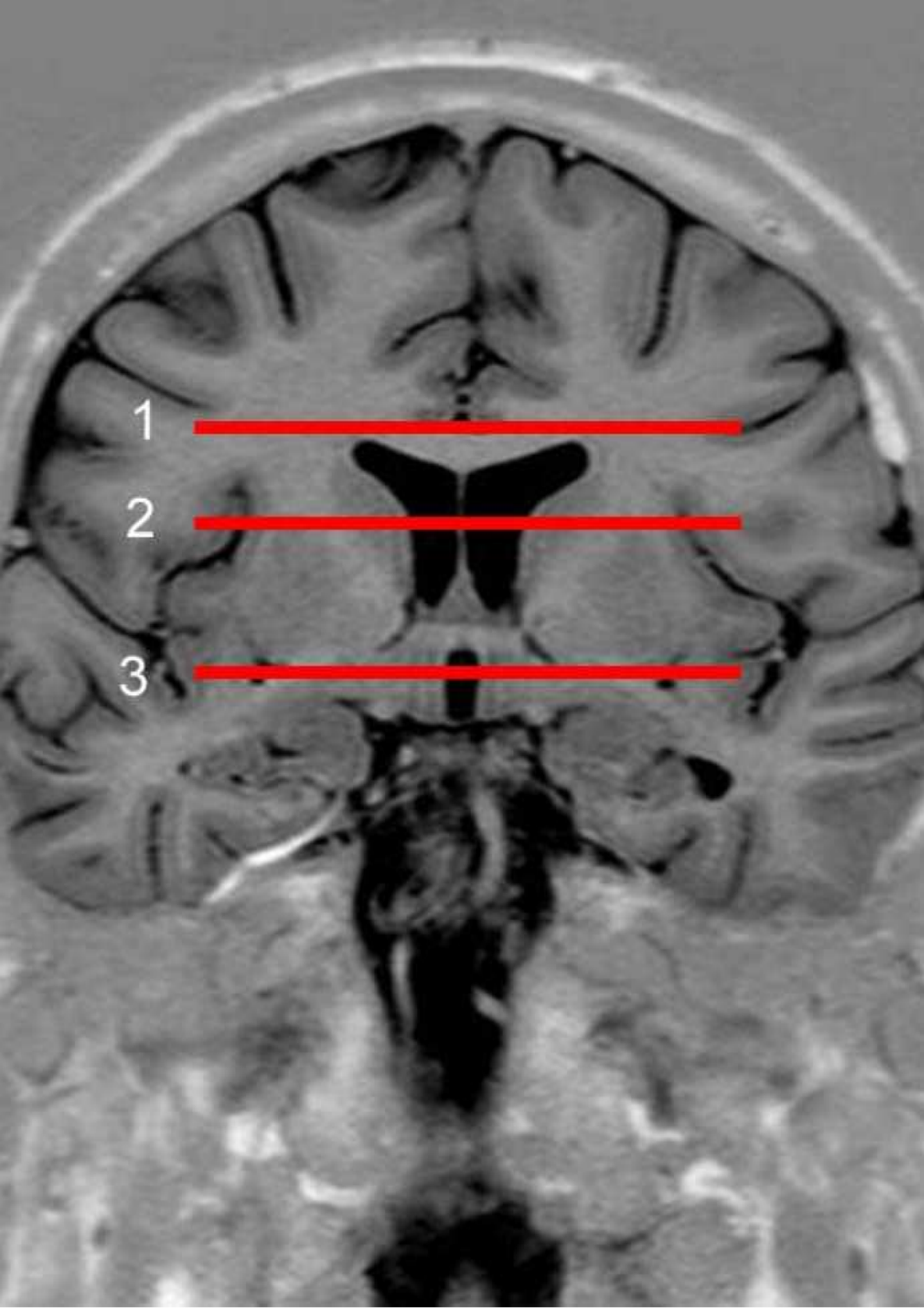
603

604 Table 5

605 Brain asymmetry from laterality, MD results, mean, median, Standard Deviation (SD) and p value (t test). R vs L (right-side):
606 looking for a significant difference between right-handers (R) and left-handers (L) based on laterality.

607

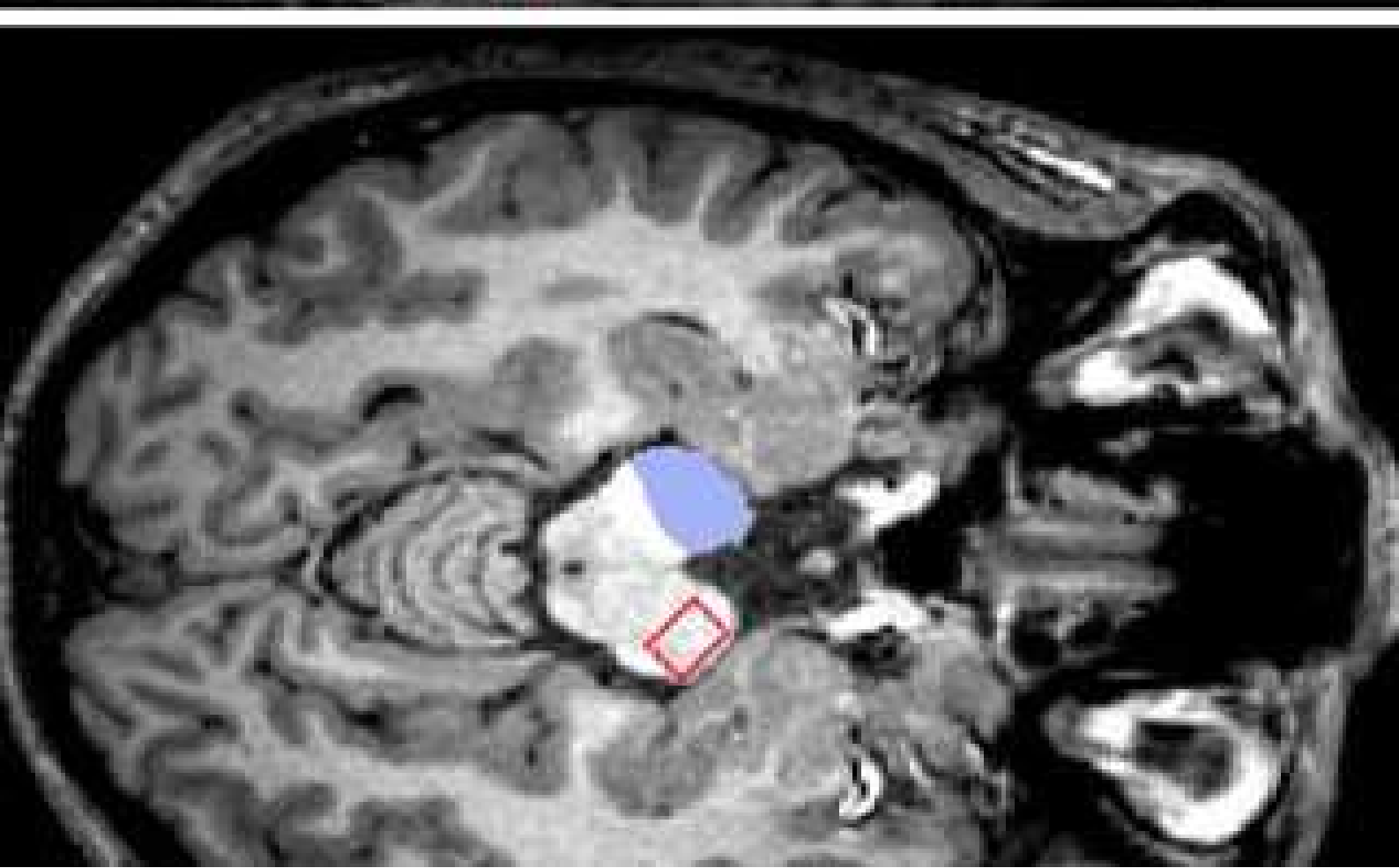
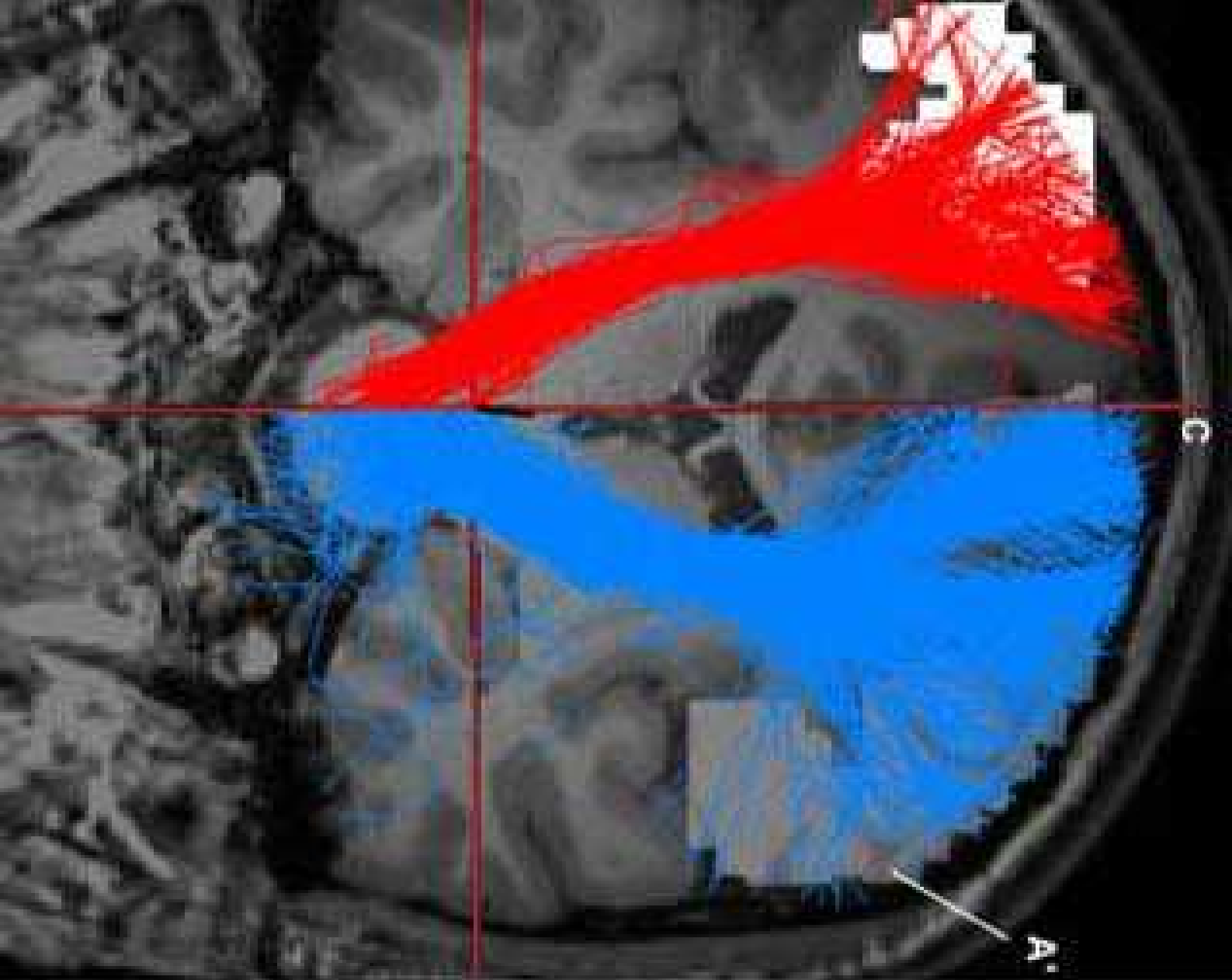
608

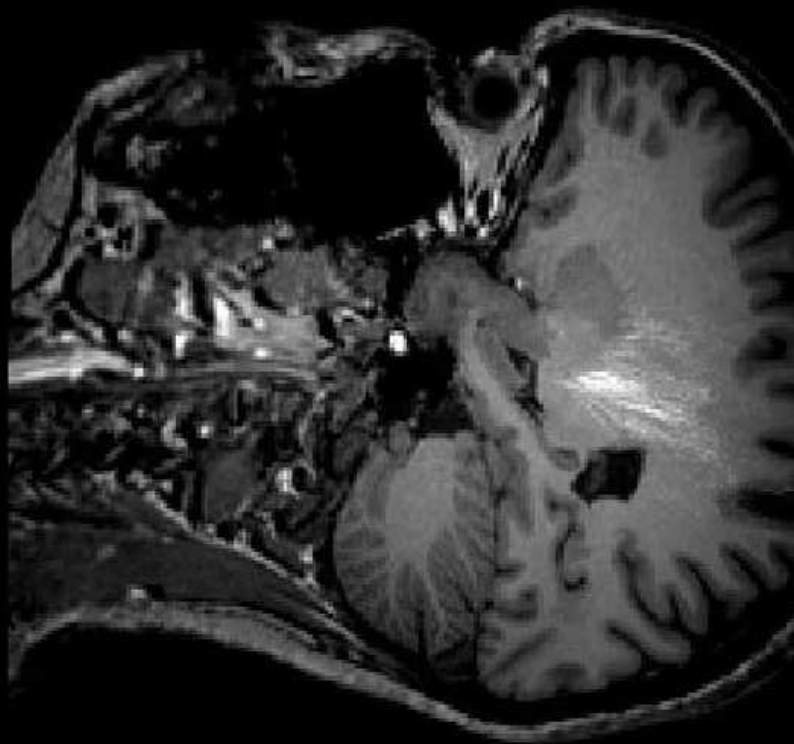
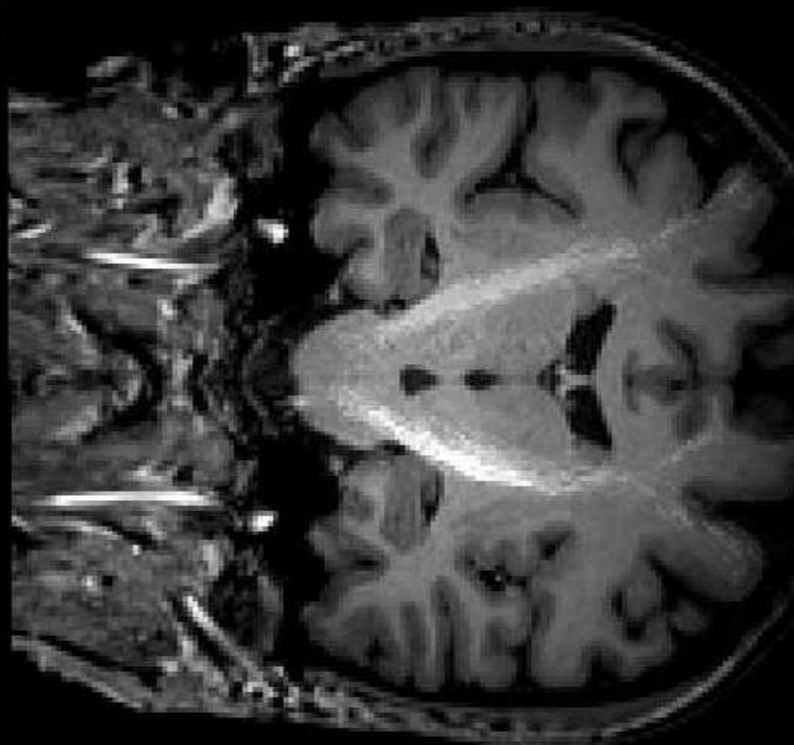
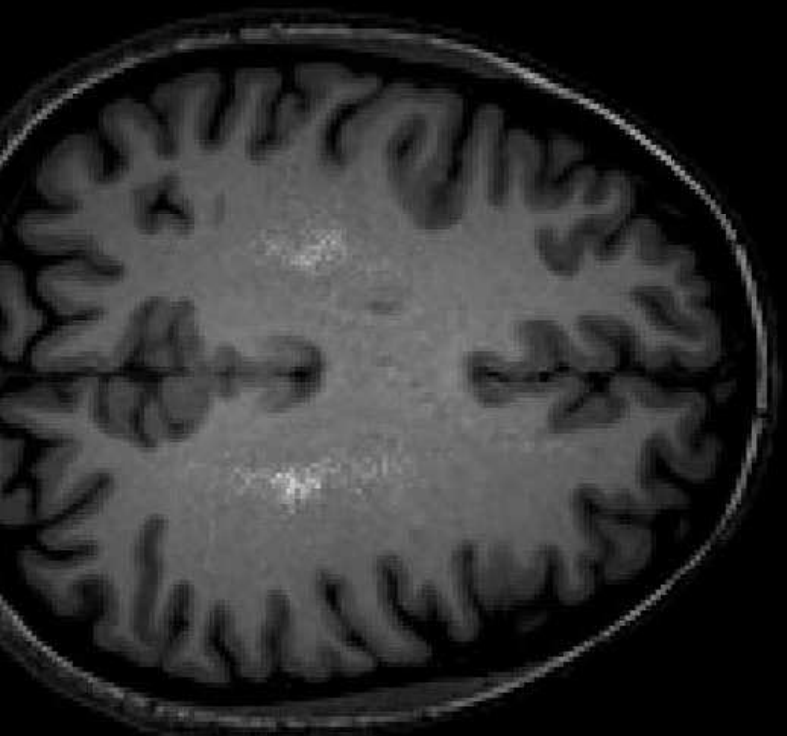
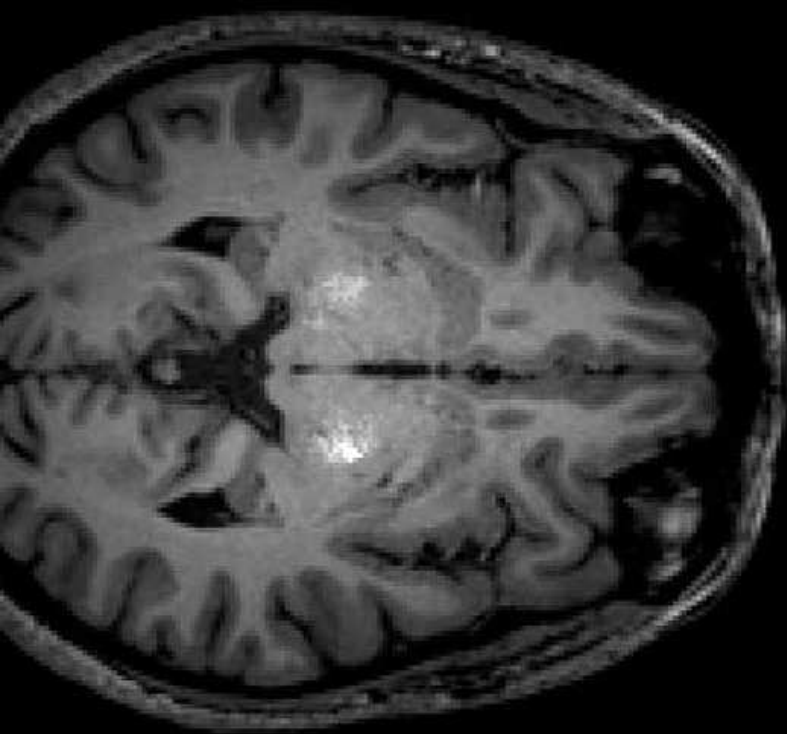


1

2

3





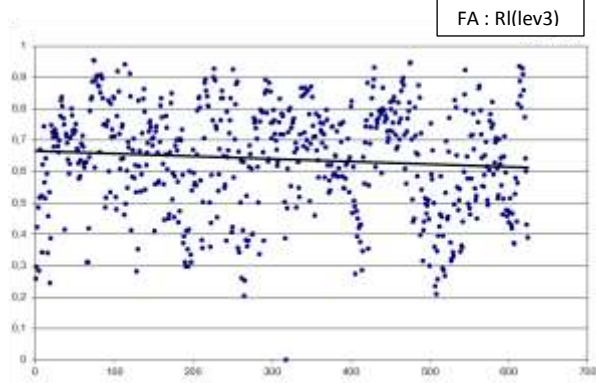
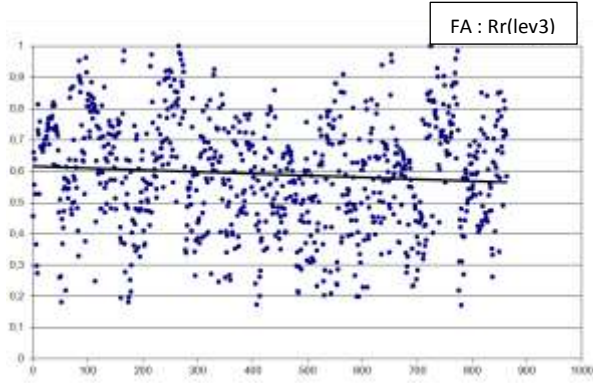
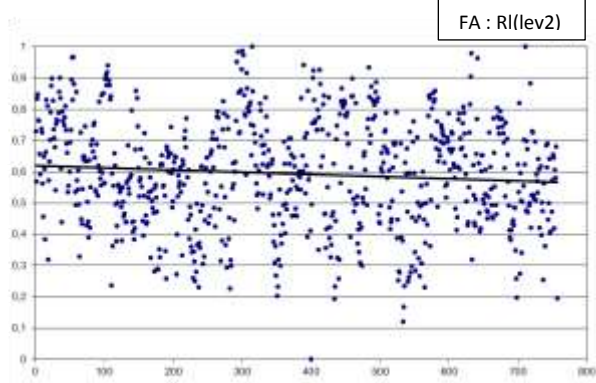
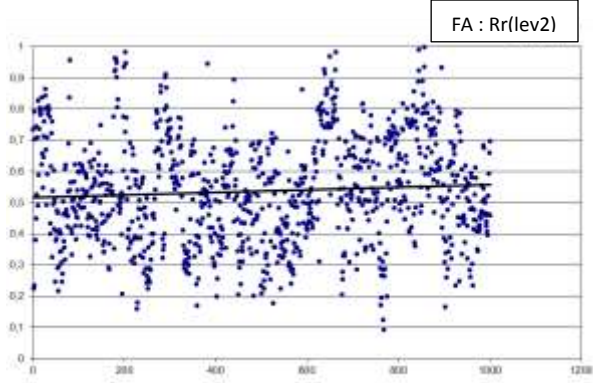
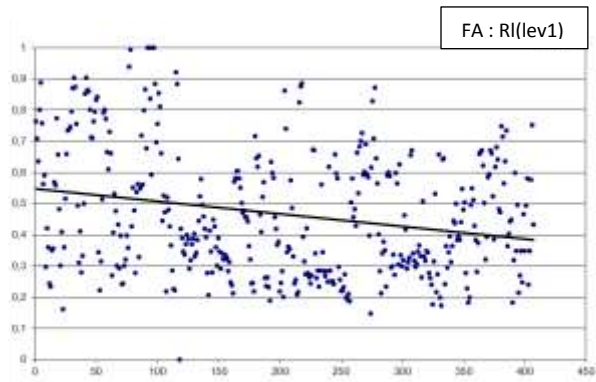
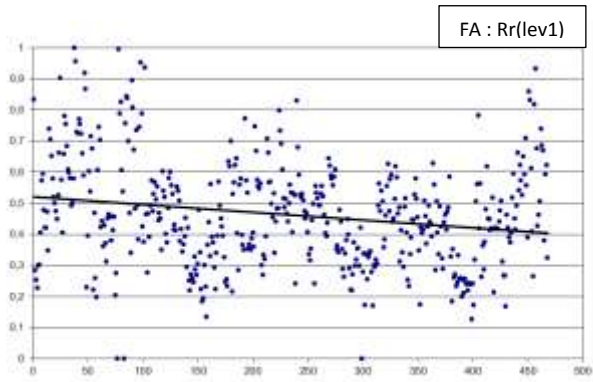


Figure 4a

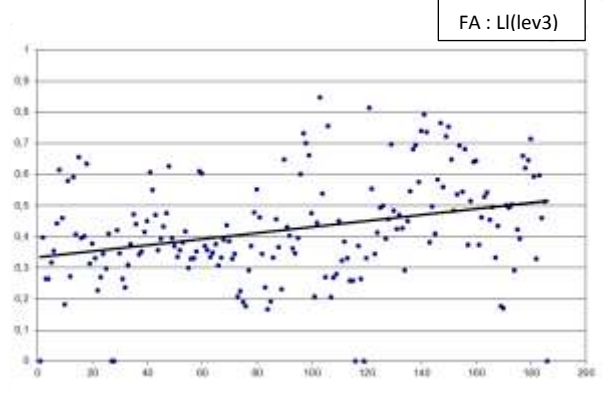
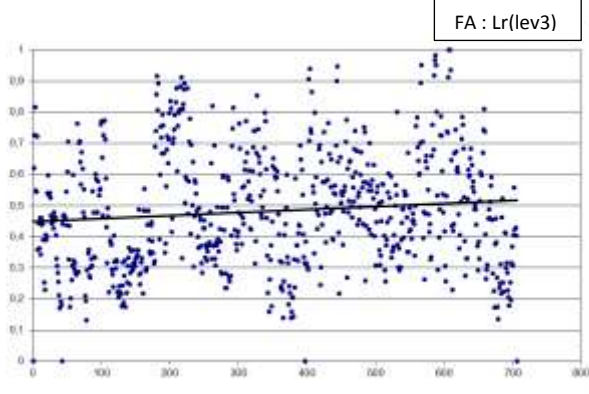
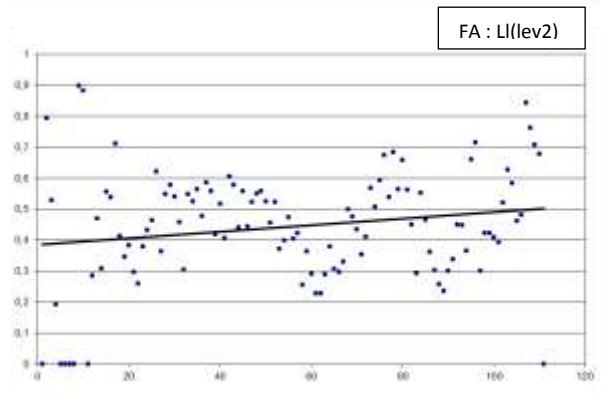
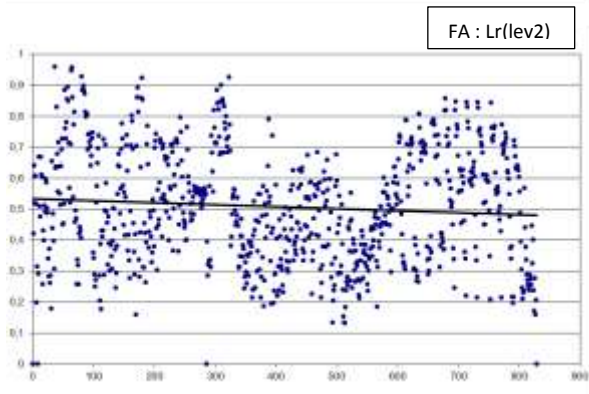
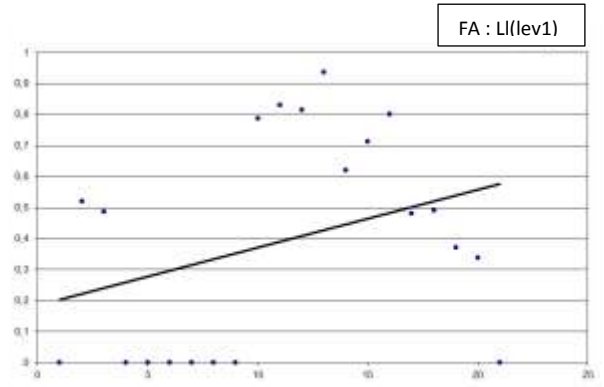
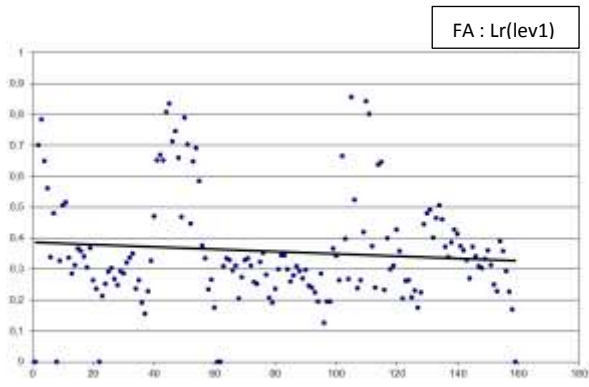


Figure 4b

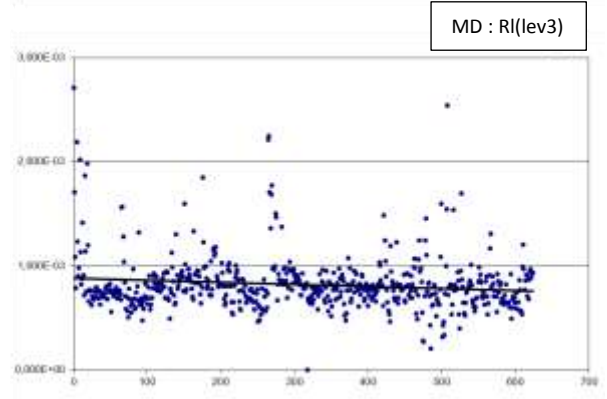
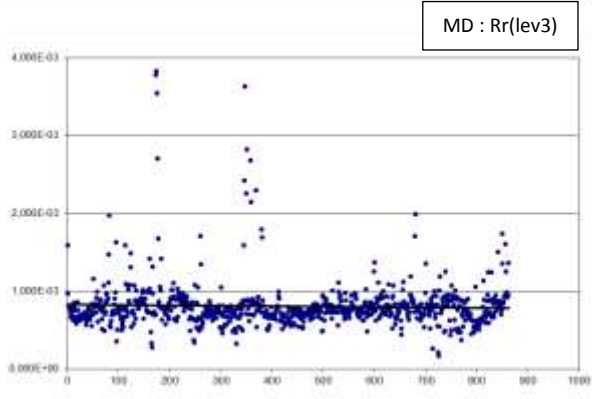
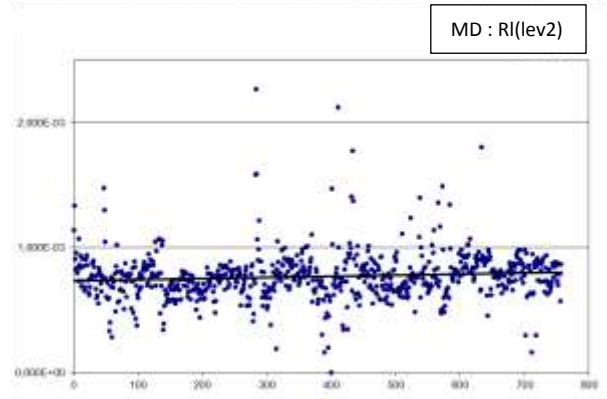
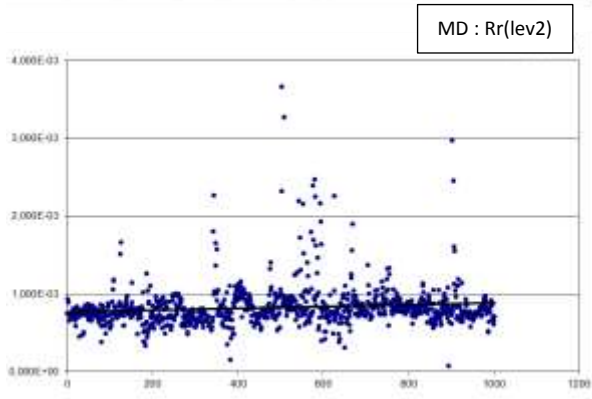
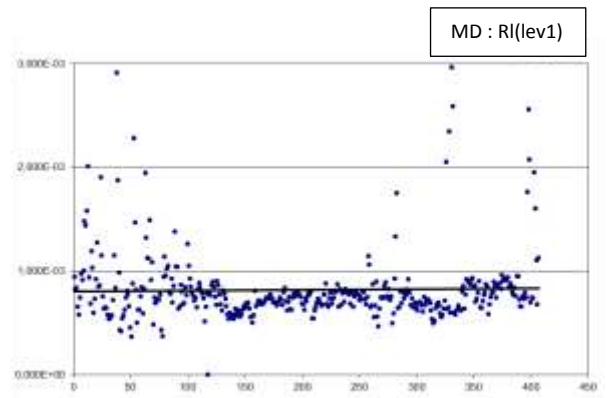
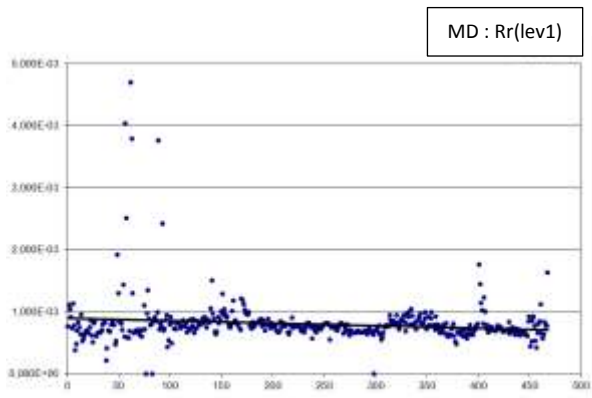


Figure 5a

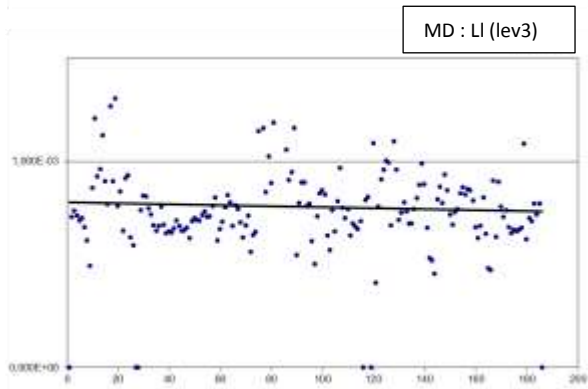
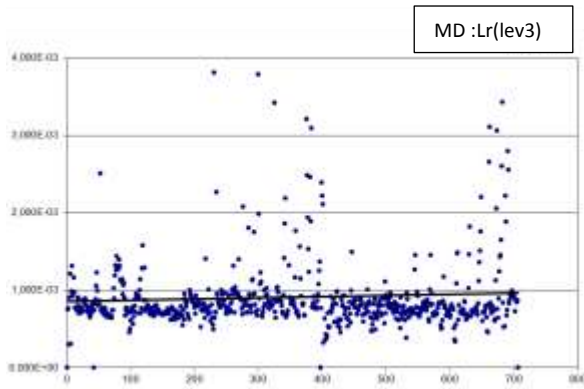
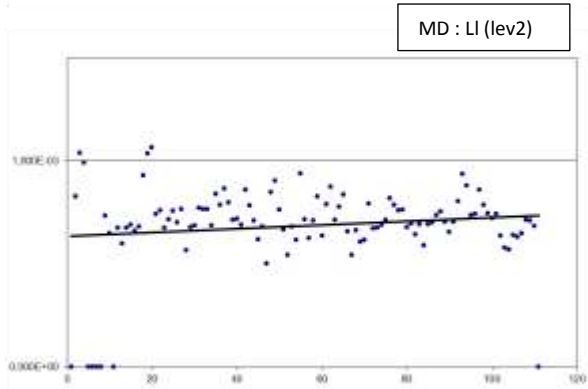
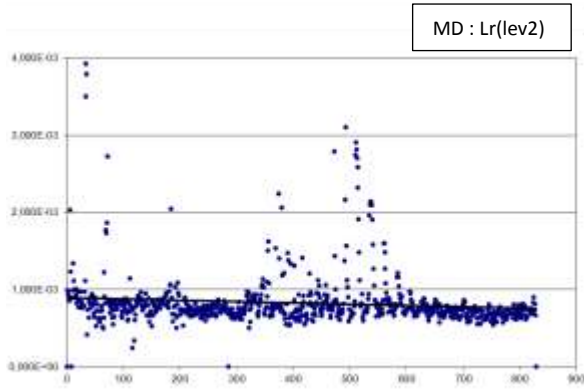
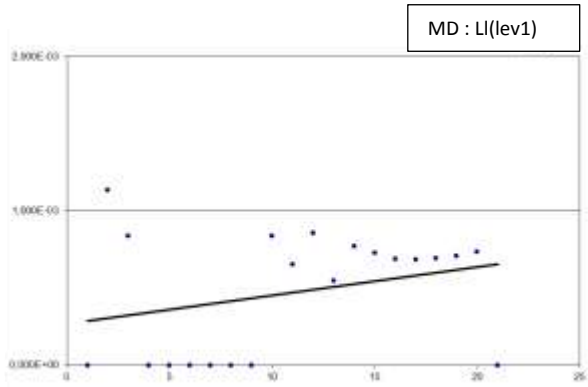
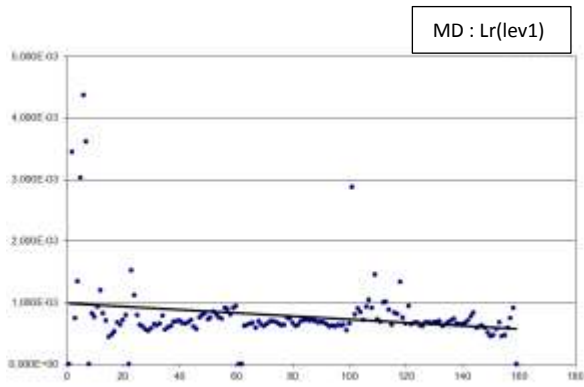


Figure 5b

Table 1

Subjects	score	laterality
1	0	R
2	0	R
3	0	R
4	0	R
5	0	R
6	1	RA
7	0	R
8	0	R
9	0	R
10	0	R
11	0	R
12	0	R
13	0	R
14	0	R
15	0	R
16	20	L
17	11	LA
18	20	L
19	14	LA
20	7	LA
21	13	LA
22	20	L
23	20	L
24	20	L
25	20	L

Table 2

R Subjects	Volume (r)	Volume (l)
1	11418	34339
2	13199	17914
3	18094	570
4	5450	8653
5	64991	14706
6	11764	23780
7	8042	12943
8	37227	4661
9	12367	11734
10	9284	22182
11	25755	19876
12	40297	48815
13	19418	50279
14	10162	700
15	19231	18376
mean	20446.6	19301.9
median	13199	17914
SD	15448.7	14678.1

L Subjects	Volume (r)	Volume (l)
16	5087	2778
17	14015	18080
18	19827	18212
19	13119	2778
20	18610	11077
21	14273	7132
22	35858	17892
23	8748	4189
24	118831	16309
25	9497	19325
mean	25786.5	11777.2
median	14144	13693
SD	32033.5	6615.5

Table 3

R Subjects	right hand	left hand
1	68	259
2	162	404
3	338	73
4	7	163
5	203	447
6	8	234
7	146	89
8	395	0
9	405	42
10	1	59
11	446	88
12	322	475
13	243	748
14	67	60
15	132	86
mean	196.2	215.1
median	162.0	89.0
SD	149.2	206.5

L Subjects	right hand	left hand
16	1	1
17	262	215
18	69	17
19	31	1
20	205	194
21	80	0
22	899	2
23	97	92
24	2804	156
25	20	34
mean	446.8	71.2
median	97.0	34.0
SD	825.0	82.1

Table 4

RK2	laterality	FA			
		Right-Handers		Left-Handers	
	hand	right	left	right	left
Level 1	minimum	0	0	0	0
	maximum	1	1	0.85596	0.93627
	mean	0.46223	0.46759	0.35706	0.39016
	median	0.45054	0.42144	0.31974	0.48064
	p value	0.671		0.6725	
	R vs L (right-side)	<0.0001			
	R vs L (left-side)	0.3237			
Level 2	minimum	0.09239	0	0	0
	maximum	0.99798	1	0.95827	0.89832
	mean	0.53480	0.59328	0.50709	0.44397
	median	0.52552	0.59975	0.50029	0.45063
	p value	<0.0001		0.0007	
	R vs L (right-side)	0.0007			
	R vs L (left-side)	<0.0001			
Level 3	minimum	0.171138	0	0	0
	maximum	1	0.95442	1	0.84667
	mean	0.58785	0.63625	0.48280	0.42517
	median	0.59605	0.66117	0.46439	0.40477
	p value	<0.0001		0.0001	
	R vs L (right-side)	<0.0001			
	R vs L (left-side)	<0.0001			

Table5

RK2	MD				
	laterality	Right-Handers		Left-Handers	
	hand	right	left	right	left
Level 1	minimum	0	0	0	0
	maximum	0.00469	0.00326	0.00437	0.00114
	mean	0.00081	0.00082	0.00078	0.00047
	median	0.00076	0.00074	0.00068	0.00068
	p value	0.6004		0.0111	
	R vs L (right-side)	0.6162			
	R vs L (left-side)	<0.0001			
Level 2	minimum	0.00008	0	0	0
	maximum	0.00366	0.00227	0.00392	0.00107
	mean	0.00083	0.00077	0.00082	0.00069
	median	0.00078	0.00076	0.00075	0.00071
	p value	<0.0001		<0.0001	
	R vs L (right-side)	0.8819			
	R vs L (left-side)	<0.0001			
Level 3	minimum	0.00017	0	0	0
	maximum	0.00383	0.00271	0.00517	0.00212
	mean	0.00082	0.00082	0.00091	0.00078
	median	0.00076	0.00078	0.00078	0.00075
	p value	0.9553		<0.0001	
	R vs L (right-side)	<0.0001			
	R vs L (left-side)	0.0868			