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

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4

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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 mm<sup>3</sup>; 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 mm<sup>3</sup>; 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  $\text{mm}^3$ ; 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/mm<sup>2</sup>). 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

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420

#### 421 **Conflict of interest**

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



423

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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 (mm<sup>3</sup>) 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.

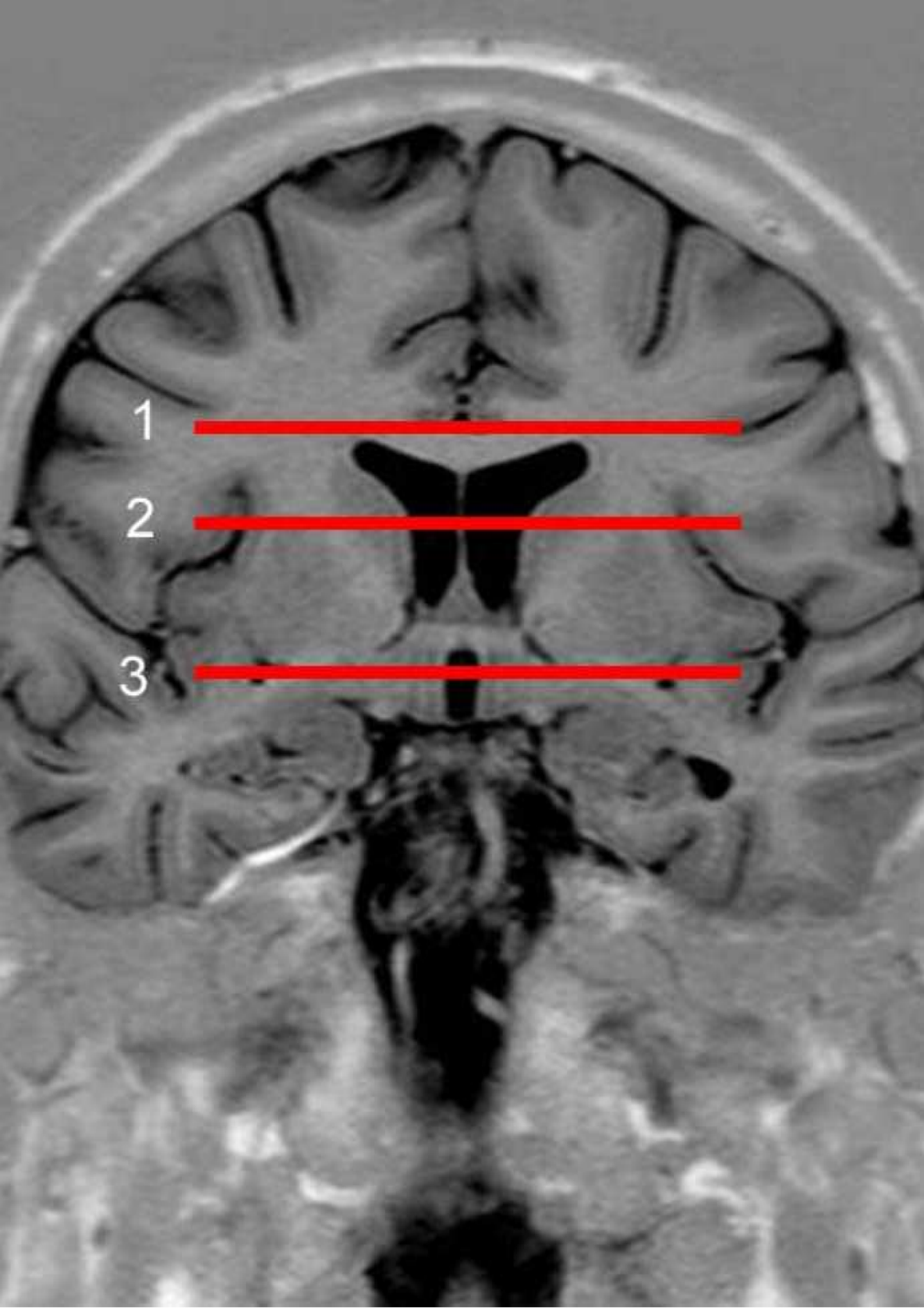
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604 Table 5

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.

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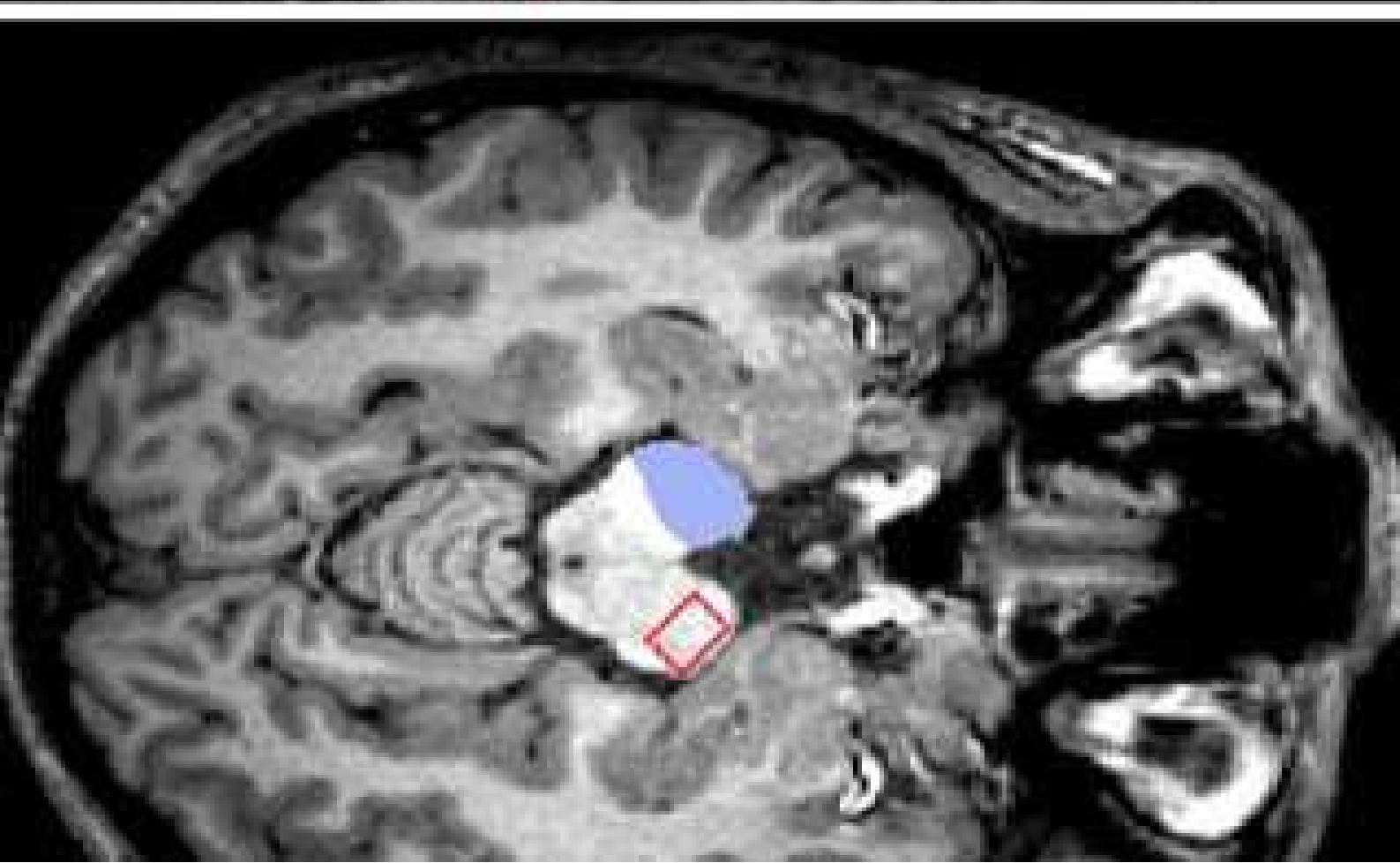
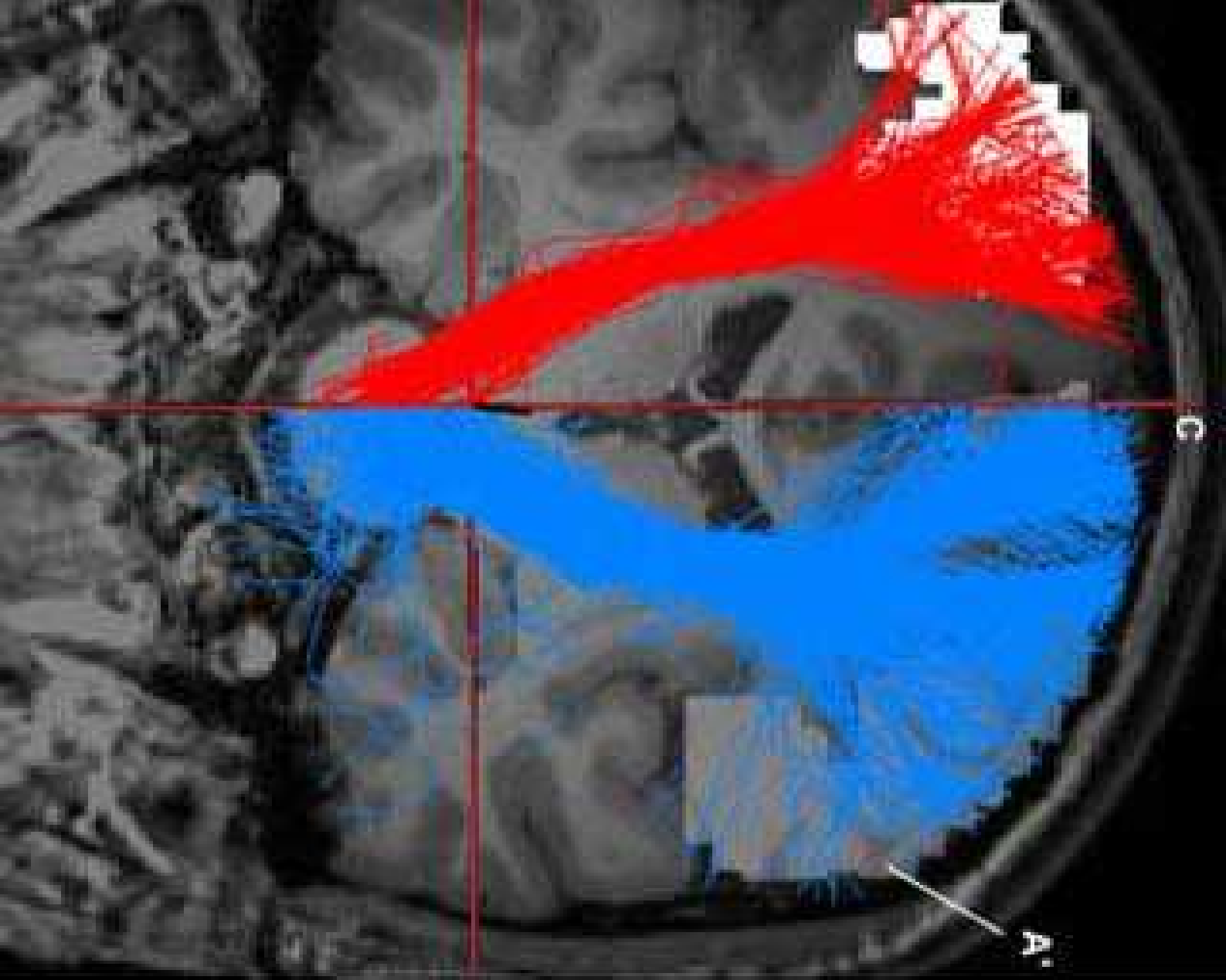
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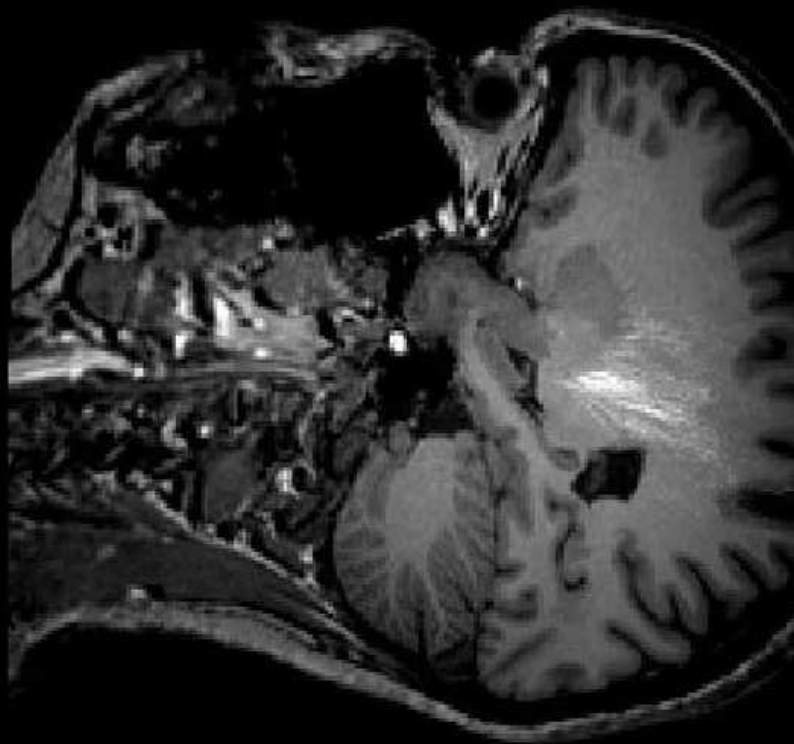
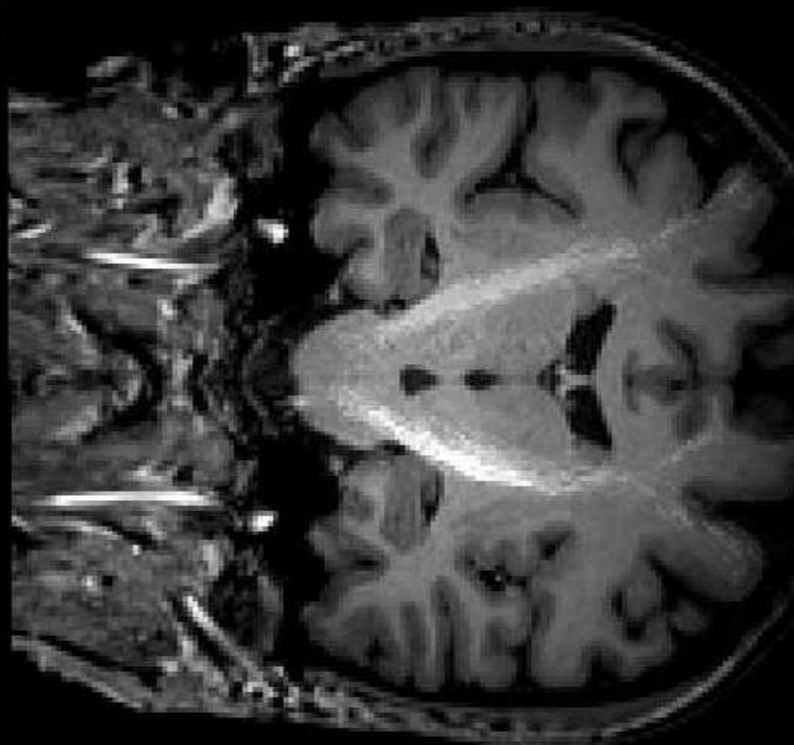
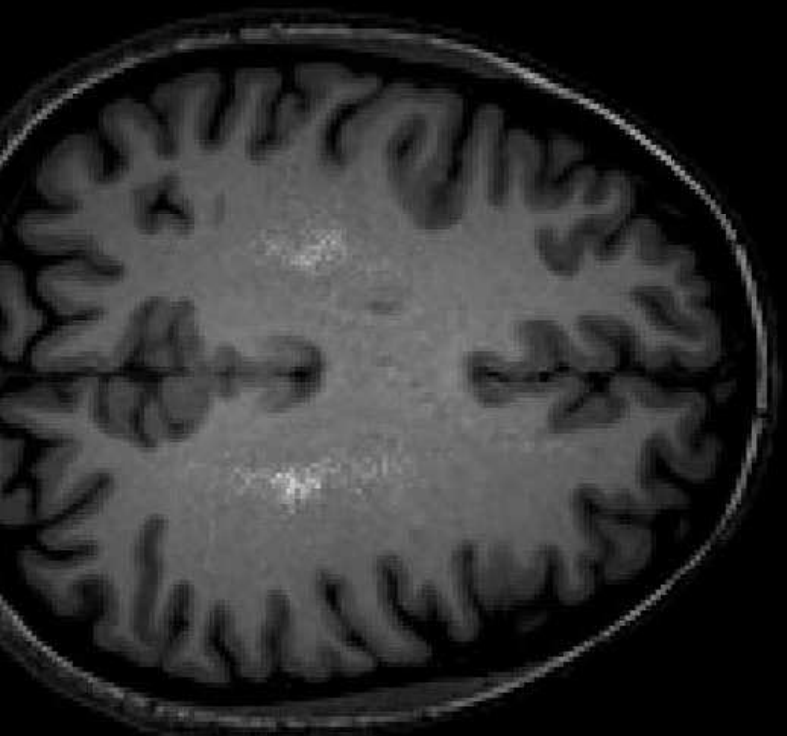
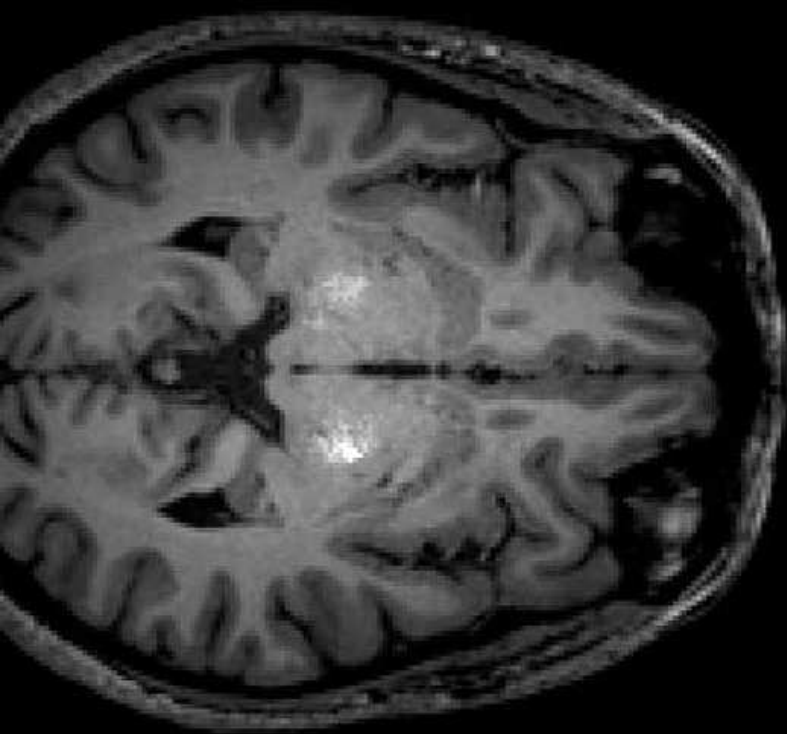
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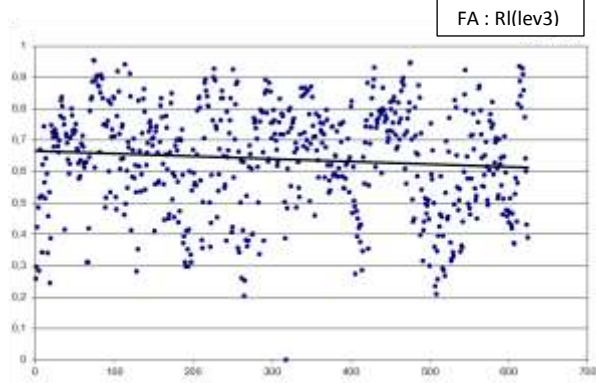
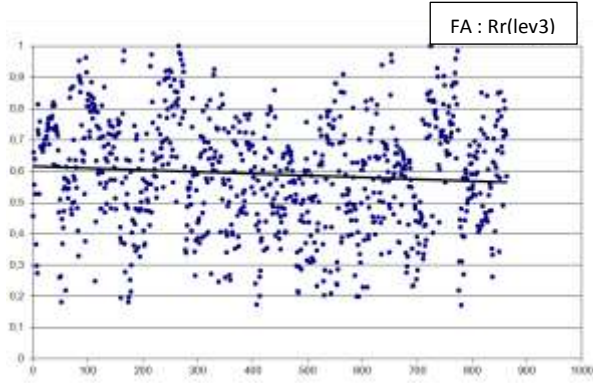
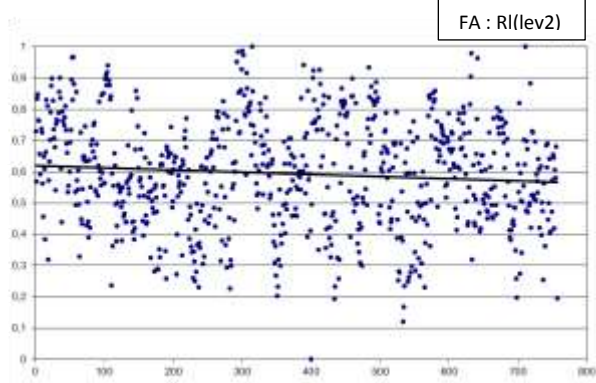
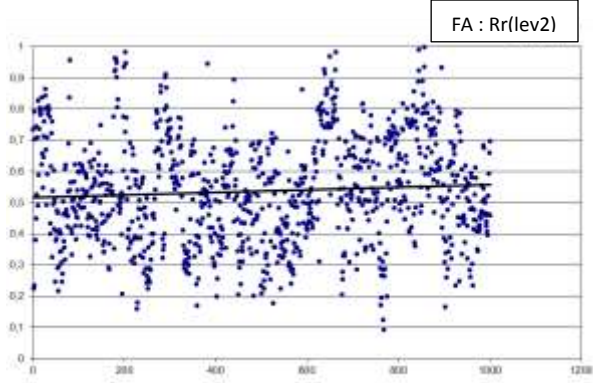
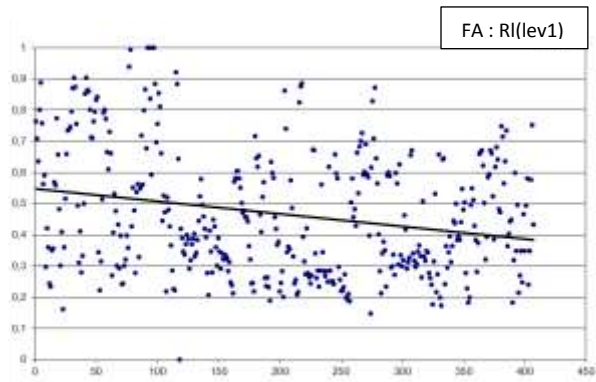
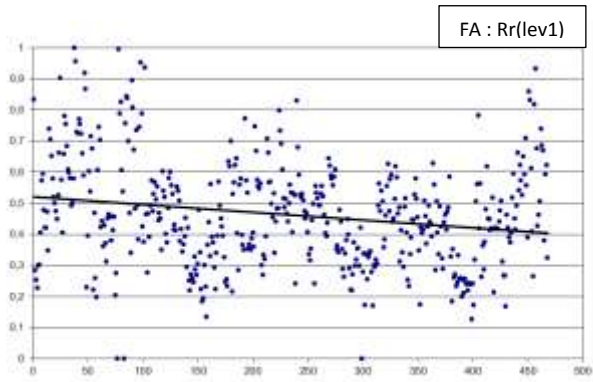


Figure 4a

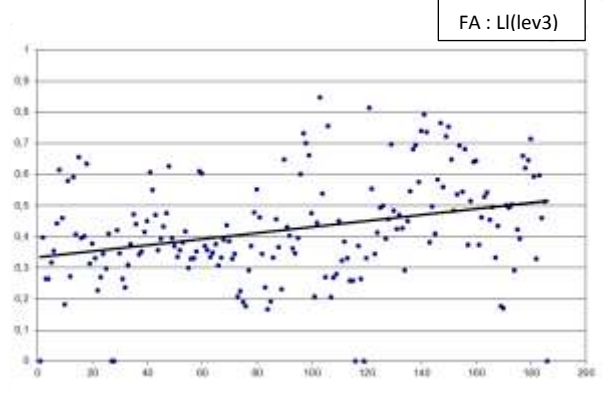
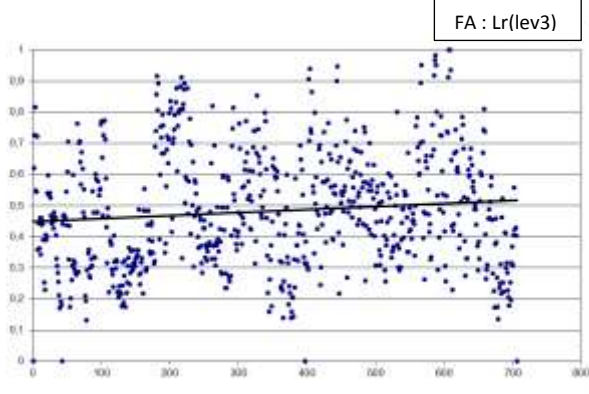
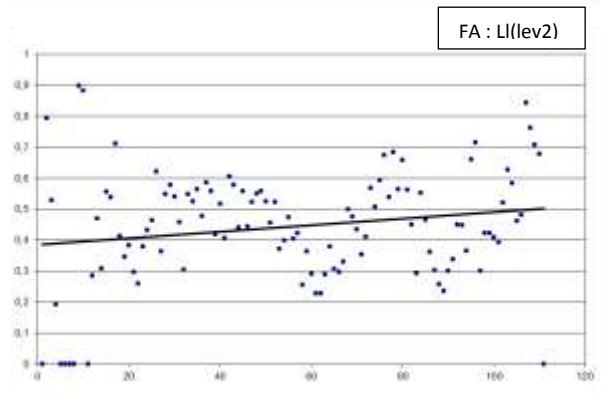
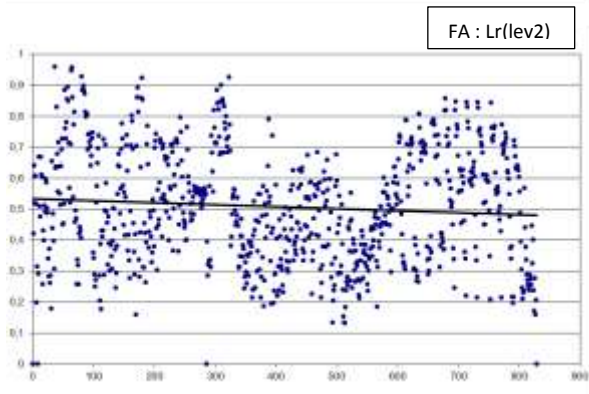
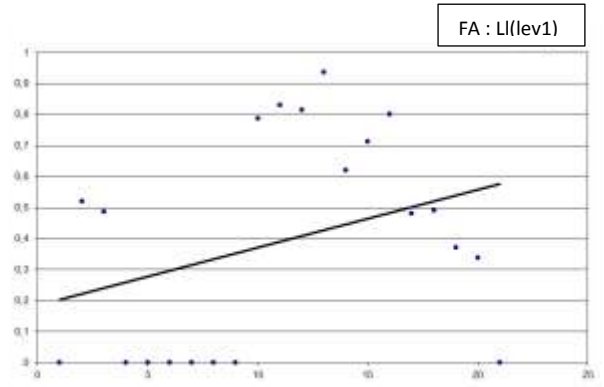
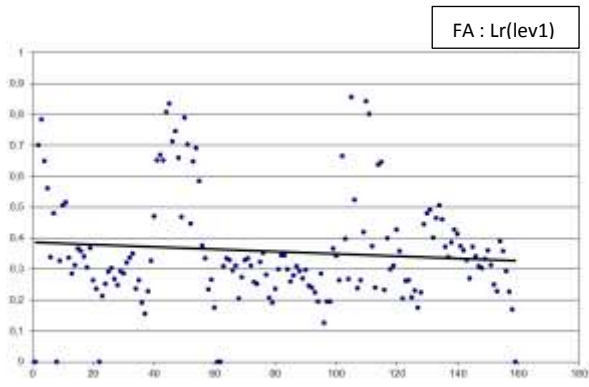


Figure 4b

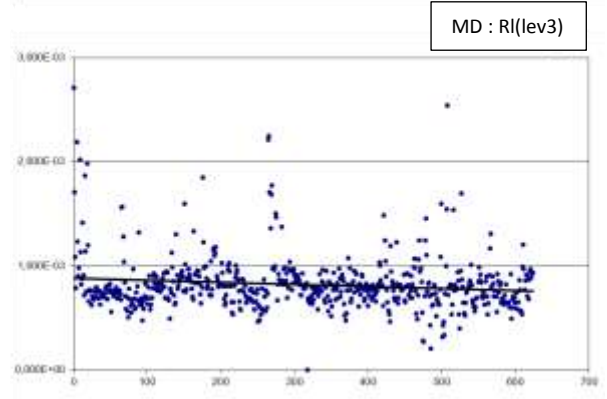
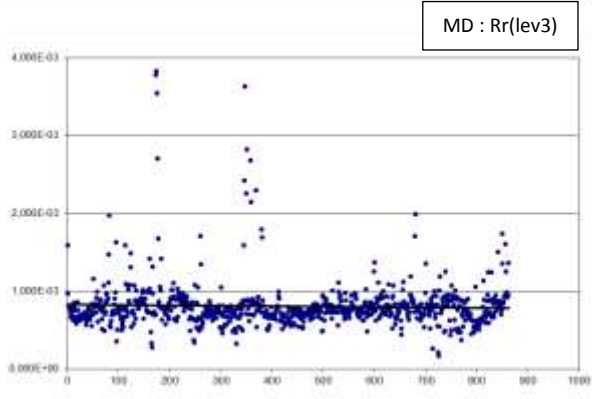
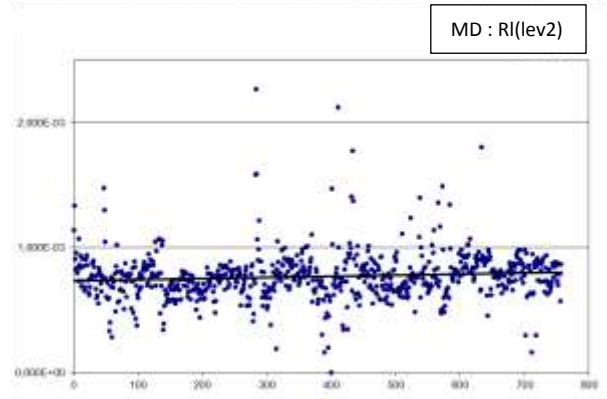
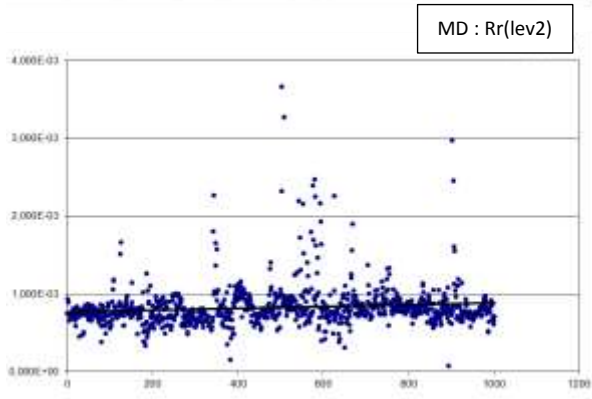
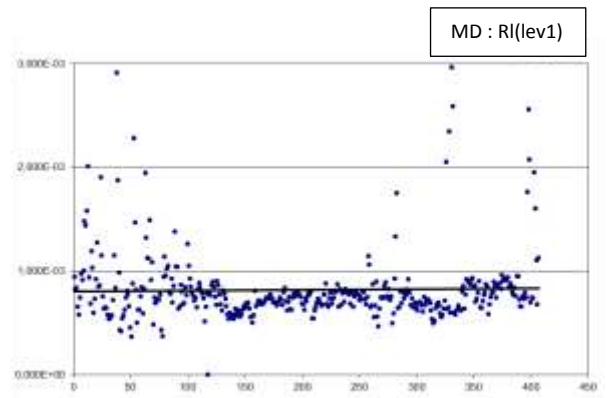
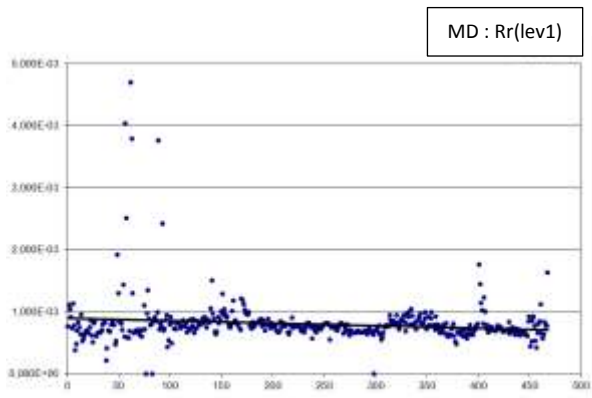


Figure 5a



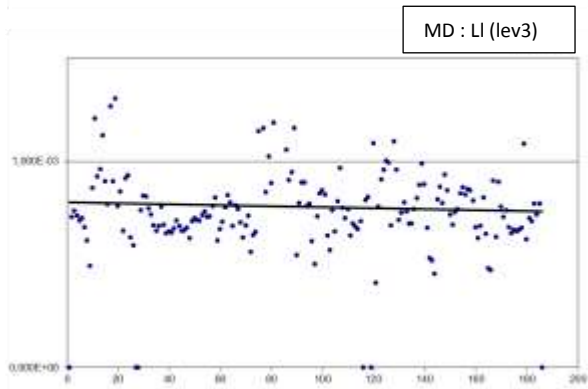
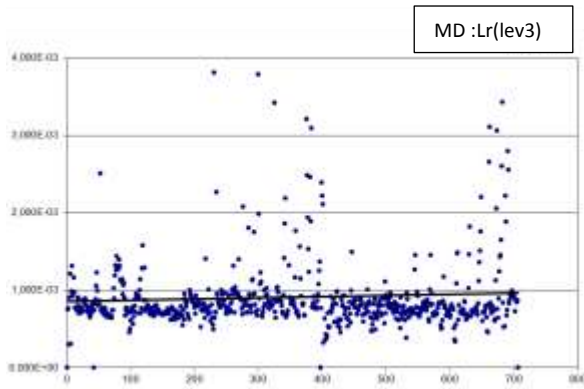
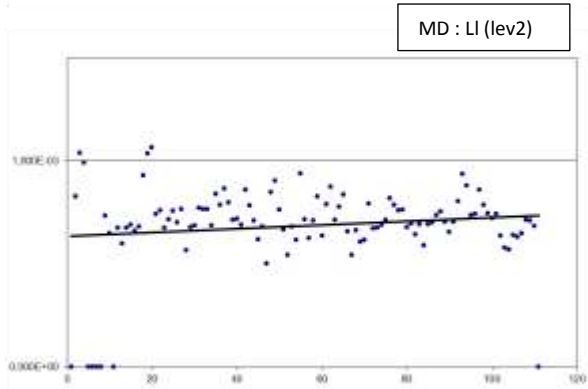
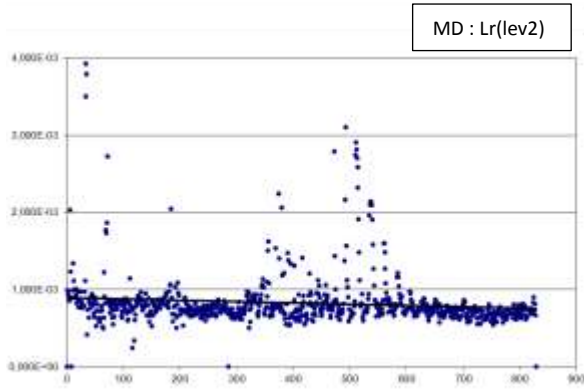
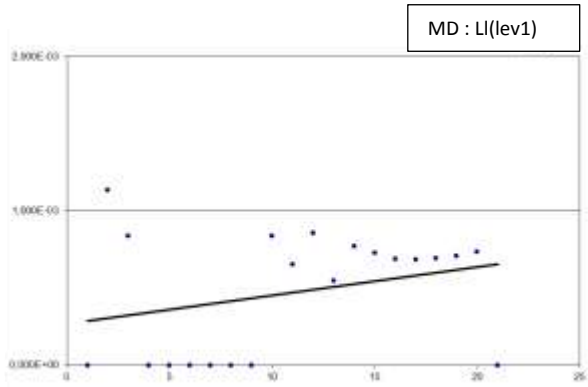
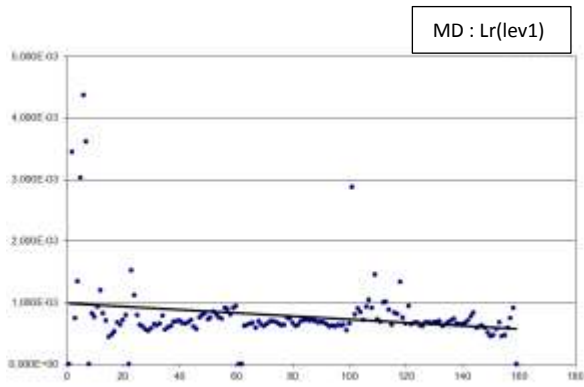


Figure 5b

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			