Cognitive performance in distinct groups of children undergoing epilepsy surgery – a single-centre experience

Barbora Benova [Equal first author, 1, 2], **Anezka Belohlavkova** [Equal first author, 1, 2], **Petr Jezdik** [3], **Alena Jahodova** [1, 2], **Martin Kudr** [1, 2], **Vladimir Komarek** [1, 2], **Vilem Novak** [1, 4], **Petr Liby** [5], **Robert Lesko** [1, 5], **Michal Tichy** [1, 5], **Martin Kyncl** [1, 6], **Josef Zamecnik** [1, 7], **Pavel Krsek** [Corresp., 1, 2], **Alice Maulisova** [8]

[1] 2nd faculty of medicine, Charles University Prague, Prague, Czech Republic

[2] Department of Paediatric Neurology, Motol University Hospital, Prague, Czech Republic

[3] Faculty of Electrical Engineering, Department of Circuit Theory, Czech Technical University of Prague, Prague, Czech Republic

[4] Department of Paediatric Neurology, Ostrava Faculty Hospital, Ostrava, Czech Republic

[5] Department of Neurosurgery, Motol University Hospital, Prague, Czech Republic

[6] Department of Radiology, Motol Universiy Hospital, Prague, Czech Republic

[7] Department of Pathology and Molecular Medicine, Motol University Hospital, Prague, Czech Republic

[8] Department of Clinical Psychology, Motol University Hospital, Prague, Czech Republic

Corresponding Author: Pavel Krsek
Email address: pavel.krsek@fnmotol.cz

Background. We aimed first to describe trends in cognitive performance over time in a large patient cohort (n= 203) from a single tertiary centre for paediatric epilepsy surgery over the period of 16 years divided in two (developing - pre-2011 vs. established – post-2011). Secondly, we tried to identify subgroups of epilepsy surgery candidates with distinctive epilepsy-related characteristics that associate with their pre- and post- surgical cognitive performance. Thirdly, we analysed variables affecting pre-surgical and post-surgical IQ/DQ and their change(post- vs. pre-surgical).

Methods. We analysed IQ/DQ data obtained using standardized neuropsychological tests before epilepsy surgery and one year post-surgically, along with details of patient's epilepsy, epilepsy surgery and outcomes in terms of freedom from seizures. Using regression analysis, we described the trend in post-operative IQ/DQ. Cognitive outcomes and the associated epilepsy- and epilepsy surgery-related variables were compared between periods before and after 2011. Using multivariate analysis we analysed the effect of individual variables on pre- and post-operative IQ/DQ and its change.

Results. Epilepsy surgery tends to improve post-surgical IQ/DQ, most significantly in patients with lower pre-surgical IQ/DQ, and post-surgical IQ/DQ strongly correlates with pre-surgical IQ/DQ (Rho=0.888, $p<0.001$). We found no significant difference in pre-, post-surgical IQ/DQ and IQ/DQ change between the periods of pre-2011 and post-2011 ($p=0.7$, $p=0.469$, $p=0.796$, respectively). Patients with temporal or extratemporal epilepsy differed in their pre-surgical IQ/DQ ($p=0.001$)and in IQ/DQ change ($p=0.002$) from those with hemispheric epilepsy, with no significant difference in post-surgical IQ/DQ ($p=0.888$). Groups of patients with different underlying histopathology showed significantly different pre- and post-surgical IQ/DQ ($p<0.001$and $p<0.001$respectively) but not IQ/DQ change ($p=0.345$).Variables associated with severe epilepsy showed effect on cognitive performance in multivariate model.

Discussion. Post-surgical IQ/DQ strongly correlates with pre-surgical IQ/DQ and greatest IQ/DQ gain occurs in patients with lower pre-surgical IQ/DQ scores. Cognitive performance was not affected by changes in paediatric epilepsy surgery practice. Pre- and post-operative cognitive performances, as well

as patients' potential for cognitive recovery, are highly dependent on the underlying aetiology and epileptic syndrome.

1   **Cognitive performance in distinct groups of children undergoing epilepsy surgery– a**
2   **single-centre experience**

4   Barbora Benova[1,8]*, Anezka Belohlavkova[1,8]*, Petr Jezdik[2], Alena Jahodova[1,8], Martin Kudr[1,8],
5   Vladimir Komarek[1,8], Vilem Novak[7,8], Petr Liby[4], Robert Lesko[4], Michal Tichy[4], Martin
6   Kyncl[5,8], Josef Zamecnik[6,8],Pavel Krsek[1,8], Alice Maulisova[3]
7
8   1: 2nd faculty of medicine, Charles University Prague, Prague, Czech Republic
9   2: Department of Paediatric Neurology, Motol University Hospital, Prague, Czech Republic
10   3: Faculty of Electrical Engineering, Department of Circuit Theory, Czech Technical University
11   of Prague, Prague, Czech Republic
12   4: Department of Paediatric Neurology, Ostrava Faculty Hospital, Ostrava, Czech Republic
13   5: Department of Neurosurgery, Motol University Hospital, Prague, Czech Republic
14   6: Department of Radiology, Motol Universiy Hospital, Prague, Czech Republic
15   7: Department of Pathology and Molecular Medicine, Motol University Hospital, Prague, Czech
16   Republic
17   8: Department of Clinical Psychology, Motol University Hospital, Prague, Czech Republic

19   *These authors contributed equally to this work.
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21   **Corresponding author:**
22   Prof. Pavel Kršek, M.D., Ph.D.
23   Head of department
24   Department of Pediatric Neurology
25   Motol Epilepsy Center
26   Charles University in Prague, 2nd Faculty of Medicine
27   Motol University Hospital
28   V Úvalu 84, 150 06 - Prague 5
29   Czech Republic
30   Phone: +420 22443 3300
31   Fax: +420 22443 3322
32   E-mail: pavel.krsek@post.cz

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47   **Abstract:**

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49   **Background.** We aimed first to describe trends in cognitive performance over time in a large
50   patient cohort (n= 203) from a single tertiary centre for paediatric epilepsy surgery over the
51   period of 16 years divided in two (developing - pre-2011 vs. established – post-2011). Secondly,
52   we tried to identify subgroups of epilepsy surgery candidates with distinctive epilepsy-related
53   characteristics that associate with their pre- and post- surgical cognitive performance. Thirdly,
54   we analysed variables affecting pre-surgical and post-surgical IQ/DQ and their change(post- vs.
55   pre-surgical).
56   **Methods.** We analysed IQ/DQ data obtained using standardized neuropsychological tests before
57   epilepsy surgery and one year post-surgically, along with details of patient's epilepsy, epilepsy
58   surgery and outcomes in terms of freedom from seizures. Using regression analysis, we
59   described the trend in post-operative IQ/DQ. Cognitive outcomes and the associated epilepsy-
60   and epilepsy surgery-related variables were compared between periods before and after 2011.
61   Using multivariate analysis we analysed the effect of individual variables on pre- and post-
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64   with lower pre-surgical IQ/DQ, and post-surgical IQ/DQ strongly correlates with pre-surgical
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66   and IQ/DQ change between the periods of pre-2011 and post-2011 (*p*=0.7, *p*=0.469, *p*=0.796,
67   respectively). Patients with temporal or extratemporal epilepsy differed in their pre-surgical
68   IQ/DQ (*p*=0.001) and in IQ/DQ change (*p*=0.002) from those with hemispheric epilepsy, with no
69   significant difference in post-surgical IQ/DQ (*p*=0.888). Groups of patients with different
70   underlying histopathology showed significantly different pre- and post-surgical IQ/DQ
71   (*p<0.001*and *p<0.001* respectively) but not IQ/DQ change (*p*=0.345). Variables associated with
72   severe epilepsy showed effect on cognitive performance in multivariate model.
73   **Discussion.** Post-surgical IQ/DQ strongly correlates with pre-surgical IQ/DQ and greatest
74   IQ/DQ gain occurs in patients with lower pre-surgical IQ/DQ scores. Cognitive performance was
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93 **Introduction**

94 Epilepsy surgery represents an established method for treatment of focal drug resistant epilepsy

95 in both children and adults (Ryvlin et al. 2014). The major aims of paediatric epilepsy surgery

96 are: to relieve the patient of debilitating seizures and anti-epileptic medication, or at least to

97 significantly decrease seizure frequency, and to prevent further decline in

98 developmental/cognitive functions, often accompanying drug resistant epilepsy (Freitag &

99 Tuxhorn 2005; Moosa & Wyllie 2017). In the past few decades, the outcome in terms of freedom

100 from seizures has either tended to improve (Hemb et al. 2010), or remained stable (Lamberink et

101 al. 2015) in large paediatric epilepsy surgery centres. Freedom from seizures has repeatedly been

102 associated with favourable cognitive outcome (Puka et al. 2017; Van Schooneveld & Braun

103 2013; Viggedal et al. 2013), even with catch-up in mental development (Freitag & Tuxhorn

104 2005).

105 In an extensive review (Van Schooneveld & Braun 2013), multiple pre-, post-surgical and

106 surgery-related variables affecting cognitive performance before and after epilepsy surgery were

107 identified, including epilepsy duration, underlying aetiology, age at surgery, seizure outcome,

108 etc. Multiple additional factors play their role in cognitive development of children with focal

109 structural epilepsy, such as the extent of the epileptogenic zone and of the zone of dysfunction,

110 the epileptiform discharges and the effects of antiepileptic medication. Their interacting effects

111 may influence patients' long-term prognosis to achieve freedom from seizures and optimal

112 cognitive development (Moosa & Wyllie 2017).

113 Longitudinal studies on seizure outcomes of children undergoing epilepsy surgery compared

114 seizure outcomes between early vs. late period of the epilepsy surgery program (Hemb et al.

115 2010; Lamberink et al. 2015). The results reflected changes in epilepsy surgery practice: the

116   advent of novel diagnostic methods (magnetoencephalography, post-processing neuroimaging

117   methods, source imagingand others) and improved surgical techniques (e.g. increased use of

118   stereo-EEG). However, none of these studies focused on differences in cognitive outcomes

119   between the two periods.

120   Most studies on cognitive outcomes of paediatric epilepsy surgery patients have been limited to

121   small patients series even though over a long follow-up period (Viggedal et al. 2012) or to

122   specific subgroups, e.g. patients with low IQ (Malmgren et al. 2008), preschool children (Freitag

123   & Tuxhorn 2005), children undergoing hemispherotomy for hemimegalencephaly (Honda et al.

124   2013). Skirrow *et al.* analysed cognitive outcomes in children with temporal lobe epilepsy and

125   provided evidence that resective epilepsy surgery leads to long-term cognitive improvement,

126   compared to medical treatment only (Skirrow et al. 2011). Lee *et al.* showed that even patients

127   with severe epileptic encephalopathy, incl. Lennox-Gastaut and West syndrome, may profit from

128   epilepsy surgery both in terms of seizure and cognitive outcome; in 73.5% of cases

129   malformations of cortical development (MCD) represented the underlying aetiology (Lee et al.

130   2014). Honda *et al.* have proven the positive effect of early hemispherotomy for

131   hemimegalencephaly on developmental outcome of post-surgically seizure-free children (Honda

132   et al. 2013).

133   A more recent longitudinal study (Sibilia et al. 2017) followed 31 children who underwent

134   epilepsy surgery and a control group of 14 medically treated paediatric epilepsy surgery

135   candidates and found no significant difference between the groups in IQ/DQ both at the

136   beginning of the study and after two years of follow-up. The developmental trajectories,

137   however, differed, and patients in the surgical group improved, while patients in the conservative

138   group showed decrease in IQ/DQ over the two-year period. The main limitation of this study,

139   however, remains its small sample size. The problems of sample size and the length of follow-up

140   period were addressed in another longitudinal study (Puka et al. 2017) that analysed cognitive

141   performance in a surgical and a non-surgical group of 97 paediatric epilepsy patients and

142   unexpectedly found no difference in cognitive performance between the groups after a follow-up

143   period of 4 to 11 years. The control group, however, was quite heterogeneous, combining

144   potential surgical candidates who refused surgery and those who were not indicated for epilepsy

145   surgery in the first place, with varying aetiologies.

146   To summarize, many studies on cognitive outcomes in paediatric epilepsy surgery patients are

147   limited by small sample size, short follow-up period, and they often fail to distinguish patients'

148   cognitive abilities according to the underlying aetiology.

149   In this study we aimed first to analyse trends in cognitive profiles of children undergoing

150   epilepsy surgery over the period of 17 years and to test whether there were differences in

151   cognitive performance (pre-surgical IQ, post-surgical IQ, or change from pre-surgical to post-

152   surgical IQ) between the early and late period of the paediatric epilepsy surgery program in our

153   tertiary clinic. Next, we assessed whether there were differences in cognitive performance

154   between the early and the late period for specific underlying aetiologies and epilepsy syndromes.

155   Finally, we aimed to identify variables affecting cognitive performance in the entire cohort.

156   **Materials &Methods**

157   Patient Selection

158   Paediatric patients (≤ 19 years of age) investigated for and having undergone epilepsy surgery in

159   Motol Epilepsy Centre between January 1st, 2000 and December 31st, 2017 with available data

160   on (i) results of pre- and post-surgical neuropsychological evaluation, (ii) seizure outcome one

161   year after epilepsy surgery in patients included in analysis of post-surgical IQ/DQ and on (iii)

162   pre- and post-surgical epilepsy- and epilepsy surgery-related variables were included in the

163   study. Patients who underwent multiple epilepsy surgeries were excluded. The dataset was

164   completed to our best knowledge; however, due to the nature and length of the study, some data

165   might have been missed. Since the study is observational in nature and no experimental

166   procedures were performed, the approval of Motol University Hospital ethics committee was not

167   required. Informed consent with the pre-surgical evaluation and epilepsy surgery was obtained

168   prior to all procedures from patients or their legal representatives.

169   Study Design

170   We retrospectively analysed pre-, post-surgical IQ/DQ and the change between post- and pre-

171   surgical IQ/DQ in relation to multiple epilepsy- and epilepsy surgery-related variables. In

172   addition, the study period was divided in two – pre-2011 and post-2011 - to compare trends in

173   cognitive outcomes between the periods of developing vs. established epilepsy surgery program,

174   similar to methodology published elsewhere (Lamberink et al. 2015). The cut-off date was set to

175   December 31st, 2010. The year 2011 was chosen as the dividing line for several reasons: it was

176   marked by the introduction of stereo-EEG as a method of long-term invasive EEG monitoring in

177   our centre, and the number of epilepsy surgery procedures stabilized after the previously

178   observed increase every year (Belohlavkova et al. 2019).

179   By comparing two periods of epilepsy surgery program, we aimed to analyse whether changes in

180   patient population (e.g. different distribution of aetiologies, epileptic syndrome, age at surgery,

181   etc.) and novel diagnostic and treatment strategies (e.g. use of stereo-EEG and advances in

182   neuroimaging) that we report elsewhere (Belohlavkova et al. 2019)were reflected in cognitive

183   performance of patients included in the study. All studied epilepsy-related variables are listed in

184   Supplementary materials. Solely for the purpose of this study we used the term "epileptic

185   syndrome" to denote either temporal, or extratemporal or hemispheric electro-clinical epileptic

186   syndrome without any relationship to the underlying structural or genetic aetiology;

187   hypothalamic hamartomas were excluded for the purpose of analysis of epileptic syndromes.

188   "Abnormal neurological finding" stands for any focal abnormality in standard neurological

189   examination. Surgery type represents the type of epilepsy surgery procedure:

190   hemispherectomy/hemispherotomy, tailored resection, lesionectomy, extended lesionectomy,

191   standardized resection (in our series exclusively anterior mesial temporal resection); surgery

192   extent denotes the extent of resection: hemispheric, focal, lobar or multilobar. Surgery location

193   may be either left-, right-sided or midline (hypothalamic hamartomas were preserved for this

194   analysis). Complications related to epilepsy surgery were classified as major or minor as

195   published elsewhere (Bjellvi et al. 2015). Types of focal cortical dysplasia (FCD) were classified

196   according to ILAE consensus classification (Blumcke et al. 2011). FCD type Ia, Ib and Ic are

197   characterized by abnormalities in radial, tangential and radial and tangential migration. FCD type

198   IIa and IIb display cytological abnormalities, including dysmorphic neurons (FCD IIa and IIb)

199   and balloon cells (FCD IIb). FCD type III occurs adjacent to another pathology: hippocampal

200   sclerosis (FCD IIIa), glial or glioneural tumour (FCD IIIb), vascular malformation (FCD IIIc) or

201   lesion acquired early in life (FCD IIId) (Blumcke et al. 2011). In one type of analysis,

202   histopathological lesions were divided in two groups: developmental vs. acquired. MCD, TSC

203   and long-term epilepsy-associated tumours (LEAT) were considered developmental, and

204   inflammatory, post-traumatic and glial scar lesions were considered acquired. Specifically for the

205   purpose of this analysis, hippocampal sclerosis was excluded, as the proportion of its

206   developmental or acquired origin has not yet been unequivocally established.

207 Neuropsychological examination was performed before the (first) surgery and at one year

208 follow-up after the resection using (according to patient´s age and cognitive level) Wechsler

209 Adult Intelligence Scale in 3rd revision(Wechsler 2010), Wechsler Intelligence Scale for

210 Children in 3rd revision(Wechsler 2002)for evaluating IQ and Bayley Scales of Infant

211 Development in 2nd revision(Bayley 1993) for developmental quotient assessment. Stanford-

212 Binet Intelligence Scale in 4th revision (Thorndike 1986) was selected for IQ testing in children

213 with lower cognitive skills (expected IQ<60), despite its limited reproducibility and reliability of

214 IQ testing in this group of patients.

215 Statistical Procedures

216 Pre-surgical and post-surgical IQ/DQ and IQ/DQ change scores were selected as dependent

217 variables. We first performed regression analysis to describe the relationship between pre- and

218 post-surgical IQ/DQ in the entire cohort and separately for children above and below 6 years of

219 age and for children above and below 12 years of age. Then, we did univariate regression

220 analysis for continuous observed (independent) variables and selected those with p-value below

221 0.05 for multivariate analysis. We performed one-way ANOVA for categorical variables and

222 calculated median difference and its 95% confidence interval using Hodges-Lehman estimator.

223 For calculation of effect sizes, omega-squared effect size was used for ANOVA tests and r-

224 squared effect size for correlation tests and multivariant models.

225 In the multivariate analysis, we calculated a multiple regression based on the general linear

226 modelby stepwise

227 regression algorithm with the variables that reached statistical significance in univariate testing.

228 The beta coefficients with p-values of <0.05 were considered statistically significant. For the

229 calculations software MatLab version 2017b and its statistical computing toolbox was used.

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231 **Results**

232 A total of 203 patients were included in the study (103 males, 100 females). For patients' details

233 see Supplementary materials and Table 1. After accounting for the missing data, 191 patients

234 were included in the analyses of pre-surgical IQ/DQ, 156 patients of post-surgical IQ/DQ and

235 154 of IQ/DQ change.

236 Trends in cognitive performance in the periods of pre-2011 vs. post-2011

237 Using regression analysis, we have shown there exists strong and significant correlation between

238 pre- and post-surgical IQ/DQ, and that patients undergoing epilepsy surgery tend to have higher

239 post-surgical IQ/DQ than pre-surgical IQ/DQ (Rho=0.888, $p<0.001$). The gain in IQ/DQ is more

240 prominent in those with lower pre-surgical IQ/DQ and the group of children older than 6 years of

241 age (Fig 1). We found no significant difference in pre-, post-surgical IQ/DQ and IQ/DQ change

242 between the periods of pre-2011 and post-2011 ($p=0.62$, $p=0.65$, $p=0.77$, respectively). When

243 analysed in groups according to the epileptic syndrome, differences in cognitive performance

244 (pre-, post-surgical IQ/DQ and IQ/DQ change) between the two periods (pre-2011 vs. post-2011)

245 were not significant for groups of patients with temporal lobe epilepsy (TLE), extratemporal

246 (XTLE) and with hemispheric (HEMI) epilepsy. The same is true in relation to underlying

247 histopathology and developmental vs. acquired lesions (see Supplementary materials). In the

248 analysis of differences between the two periods, we classified FCD in three classes (FCD type I,

249 FCD type II, FCD type III) as the small numbers in respective subcategories (FCD type Ia-Ic, IIa

250 and IIb and IIIa-IIId) would preclude statistical calculation. We found a significantly lower pre-

251 and post-surgical IQ/DQ in the period post-2011 (F=8.28, $p=0.013$ and F=4.76, $p=0.05$,

252 respectively) in the group of FCD type I. We did not identify significant difference in post-

253 surgical IQ/DQ and IQ/DQ change between the two periods in either seizure-free or non-seizure-

254 free patient cohort (seizure free: F=0.48 p=0.49 and F=0.24, p=0.62, respectively, non-seizure-

255 free: F=0.8 p=0.38 and F=0.26 p=0.62). For statistical details, including measures of effect size

256 and degrees of freedom, see Supplementary materials.

257 Pre- and post- surgical cognitive performance in distinct groups of patients according to their

258 epilepsy-related features

259 Using ANOVA statistics we observed that patients with TLE differ from those with XTLE and

260 those with HEMI epilepsy in their pre-surgical IQ/DQ (F=6.83, p=0.001) and in their IQ/DQ

261 change (F=6.63, p=0.002); post-hoc tests showed that patients with HEMI score significantly

262 lower in their IQ/DQ compared to those with XTLE and TLE (Fig2). Depending on their

263 underlying histopathology, the analyses have identified group differences in pre- and post-

264 surgical IQ/DQ (F=6.56, p<0.001 and F=7.44, p<0.001, respectively). Post-hoc analyses found

265 significantly higher pre-surgical IQ/DQ in patients with tumour (LEAT) compared to those with

266 MCD (p=0.002), TSC (p<0,001) and glial scar (p=0.005). Significant differences in post-surgical

267 IQ/DQ were also observed between the aetiological sub-groups; patients with LEAT achieve

268 significantly higher IQ/DQ scores than those with e.g. MCD, TSC, and those with hippocampal

269 sclerosis score higher than patients with TSC. When comparing developmental vs. acquired

270 histopathological lesions we found no significant difference in their pre-, post-surgical IQ/DQ

271 and IQ/DQ change (data not shown). Furthermore, we analysed the differences in cognitive

272 performance relative to FCD classes (Blumcke et al. 2011), and found significant difference

273 between the classes in the pre- and post-surgical IQ/DQ (F=4.89, p<0.001 and F=4.73, p<0.001,

274 respectively); the results remained significant for post-surgical IQ/DQ for the classes of FCD

275   type I, II and III (F=6.32, *p*=0.003).We observed a trend towards higher pre-surgical IQ/DQ and

276   IQ/DQ change in FCD type III vs. FCD type II and type I (Fig1).

277   Predictors of pre- and post-surgical IQ/DQ and its change over the entire period

278   The results of univariate testing are listed in Table 2 for categorical variables and in Table 3 for

279   continuous variables associated with pre-surgical IQ/DQ, post-surgical IQ/DQ and IQ/DQ

280   change; only the variables significant in univariate testing are shown here, all studied variables

281   are listed in Supplementary materials. The used stepwise regression algorithm excludes variables

282   that might skew results in the calculation process of the multiple regression based on the general

283   linear model; therefore, some variables, despite being significant in univariate testing, do not

284   appear in the results of multivariate testing, listed in Table 4. Some variables associated with

285   severe epilepsy, e.g. the presence of infantile spasms affecting pre-surgical IQ/DQ remained

286   significant in univariate testing only. The factors found significant in multiple regression model

287   were (i) the presence of abnormal neurological finding and FCD type IIb and IIIb and younger

288   age at first seizure affecting pre-surgical IQ/DQ; (ii) age at first seizure, status epilepticus,

289   multilobar resection, unilobar resection, complete resection and TSC affecting post-surgical

290   IQ/DQ; (iii) age at surgery and temporal or extratemporal epileptic syndrome affecting IQ/DQ

291   change (see Table 4). The date of surgery, reflecting change in epilepsy surgery practice, was not

292   rendered significant in the multivariate regression analysis model and was therefore excluded

293   from the model by the used stepwise algorithm.

294   For the summary of statistically significant results of all tests, including post-hoc analyses and

295   the respective *p* values, F values, effect sizes and degrees of freedom, see Tables 1-5.

296   **Discussion**

297   In the period of 2000-2017 we collected data on 203 children who underwent resective epilepsy

298   surgery in the paediatric part of Motol Epilepsy Centre and studied their cognitive performance

299   in relation to the epilepsy- and epilepsy surgery-related characteristics and seizure outcome.

300   We have observed a strong correlation between the pre- and post-surgical IQ/DQ, in accordance

301   with multiple previous studies that have shown pre-surgical IQ/DQ to be a strong independent

302   predictor of post-surgical IQ/DQ (Puka et al. 2017; Van Schooneveld & Braun 2013). Our results

303   also confirm previously reported observations that epilepsy surgery leads to greater increase in

304   IQ/DQ in children with lower pre-surgical IQ/DQ (Puka et al. 2017). Loddenkemper *et al.* have

305   shown similar results in infants <3 years of age who presented with lower DQ scores and

306   infantile spasms and achieved significantly higher DQ scores after surgery. The increase

307   however was especially prominent in children operated on before 1 year of age (Loddenkemper

308   et al. 2007). The authors suggest the increase might result from the fact that the deleterious

309   epileptic activity had been terminated early enough to impede development. Therefore, we

310   presume, it is not the value of IQ/DQ *per se* that leads to cognitive improvement after surgery

311   but rather the early indication of epilepsy surgery in infants presenting with severe epilepsy and

312   developmental delay. Cognitive performance of children who enter epilepsy surgery programs

313   with normal or above-average IQ tends neither to improve, nor to worsen with epilepsy surgery.

314   Although the actual numerical increase in IQ/DQ scores did not reach clinically significant

315   values of 8-15 points (Van Schooneveld & Braun 2013), based on the regression curve equation,

316   this might have been mostly due to the limited follow-up period. Our results however, are in line

317   with other studies showing that IQ/DQ scores tend to remain stable or improve after epilepsy

318   surgery in children over a broad spectrum of cognitive performance, and even children with low

319   pre-surgical IQ/DQ do not lose cognitive skills but rather benefit from epilepsy surgery

320   (Loddenkemper et al. 2007; Viggedal et al. 2012; Viggedal et al. 2013). Unexpectedly, we

321   observed greater gain in IQ/DQ scores in children above 6 years of age (Fig. 1), compared to

322   their younger counterparts. Given that these children were operated on later, they also might

323   have had later epilepsy onset, and the effect of drug resistant seizures was not present in early

324   sensitive periods of brain development. Also, the group of children below 6 years of age was

325   rather small which might have skewed the results. In addition, the effect of repeated

326   measurement cannot be completely ruled out (Sherman et al. 2003).

327   Cognitive performance in children undergoing epilepsy surgery did not change between the

328   periods of pre-2011 and post-2011

329   Comparing cognitive performance of all epilepsy surgery patients from the period of pre-2011

330   vs. post-2011 their pre-, post-surgical IQ/DQ and IQ/DQ change scores did not differ

331   significantly. These findings might imply that the spectrum of epilepsy surgery patients has not

332   changed significantly with respect to their cognitive performance. We further analysed whether

333   distinct groups of patients in terms of epileptic syndrome and underlying aetiology differed in

334   their cognitive performance between the two studied periods and again found no significant

335   difference. These results reflect in part the development of paediatric epilepsy surgery practice in

336   the region and in Europe (Baud et al. 2018); we are seeing increased referral of more complex

337   patients and a changing population of paediatric epilepsy surgery candidates. While in the early

338   period we encountered either very severe cases (epilepsy surgery as "the last resort") or very

339   straightforward ones (e.g. hippocampal sclerosis) with a very broad span of cognitive

340   performance, in the later period we observed a decline in the straightforward cases (such as

341   hippocampal sclerosis) and an increase in timely referral of complex cases (such as TSC, see

342   Supplementary materials). The shift towards more complex patients, including extratemporal and

343 MRI negative cases, has been observed in centres around Europe (Baud et al. 2018), and this

344 might have been reflected in the cognitive performance of epilepsy surgery patients. Naturally,

345 we cannot exclude the effect of small sample size in certain aetiological groups with less

346 frequent pathologies. To summarize, the aetiological spectrum of epilepsy surgery candidates has

347 changed significantly in terms of the underlying aetiology (see Supplementary materials and

348 (Belohlavkova et al. 2019)) but the overall IQ/DQ scores remained similar.

349 Cognitive performance of children undergoing epilepsy surgery varies based on aetiology and

350 epileptic syndrome

351 Given the broad spectrum of epileptic syndromes and underlying aetiologies in the studied

352 population we hypothesised that these patients enter pre-surgical evaluation as distinct groups

353 with distinct cognitive performances. According to our analyses, patients with hemispheric

354 syndromes perform significantly lower in their IQ/DQ scores than their counterparts with

355 temporal or extratemporal epilepsy; however, they also have the greatest potential for post-

356 surgical increase in IQ/DQ scores, compared to patients with TLE or XTLE. These results are in

357 line with the results from previous studies showing that patients with hemimegalencephaly profit

358 from early epilepsy surgery (Bulteau et al. 2013; Honda et al. 2013). Considering the aetiological

359 spectrum of epilepsy surgery patients we hypothesised that patients with developmental

360 structural lesions, such as TSC, MCD or long-term epilepsy-associated tumours differ from those

361 with acquired lesions (e.g. inflammation, glial scar, etc.), but our data showed the opposite. It is

362 rather the specific aetiology itself and the extent of involvement (temporal vs. extratemporal vs.

363 hemispheric epilepsy) that distinguish these patients from each other. Patients with benign

364 tumours achieve significantly better pre- and post-surgical IQ/DQ scores than those with other

365 developmental abnormalities, e.g. TSC or MCD. Given their tendency to reach favourable

366   seizure outcome, in addition to good cognitive outcome, they represent a group that might

367   benefit from early referral to epilepsy surgery (Ramantani et al. 2014). Patients with TSC, on the

368   other hand, tend to suffer from developmental delay spanning from mild cognitive impairment to

369   profound intellectual disability in 14% to 31% respectively (Joinson et al. 2003). Despite on-

370   going discussions about the pathogenesis of cognitive impairment in TSC (Curatolo et al. 2016;

371   Chu-Shore et al. 2010), most authors agree that adequate seizure control, achieved by

372   antiepileptic medication or epilepsy surgery, in TSC patients leads to improved cognitive

373   outcomes (Arya et al. 2015; Chu-Shore et al. 2010).

374   In histopathological FCD subgroups, we observed a tendency towards better cognitive

375   performance in FCD type III, with the most significant difference in relation to FCD type I.

376   Lower IQ/DQ scores and worse outcomes of epilepsy surgery have been repeatedly observed in

377   patients with FCD type I in contrast to FCD type II (Krsek et al. 2008; Krsek et al. 2009). FCD

378   type III has only recently been distinguished as a separate category of FCD (Blumcke et al.

379   2011); therefore, it is difficult to compare the results of more and less recent studies.

380   Nevertheless, FCD type III from its definition associates with other pathologies, e.g.

381   hippocampal sclerosis (FCD IIIa) or brain tumour (FDC type IIIb), and patients with these

382   pathologies achieved higher IQ/DQ scores which also explains the observed results. We

383   observed lower pre- and post-surgical IQ/DQ in the period post-2011 in the group of FCD type I;

384   this might be a result of the rather small sample size (n=15). Another plausible explanation is

385   that we tend to accept patients with more severe epilepsy and its related adverse cognitive

386   sequelae in the epilepsy surgery program. It remains to be discovered whether and to what extent

387   molecular genetic changes in patients with FCD influence their prognosis in terms of both

388   seizure and cognitive outcome (Baldassari et al. 2018; Benova & Jacques 2018).

389 Multiple factors influence cognitive performance in children undergoing epilepsy surgery

390 In the entire patient cohort we have identified multiple factors that might affect their cognitive

391 performance. Factors associated with severe epilepsy, including early age at onset, frequent

392 seizures, occurrence of infantile spasms and status epilepticus seemed to be associated with

393 lower pre-surgical IQ/DQ scores. Given that patients suffering from infantile spasms tend to

394 improve in their cognitive skills after successful epilepsy surgery (Asarnow et al. 1997) low

395 IQ/DQ scores should not preclude timely referral for epilepsy surgery. In fact, patients with low

396 pre-surgical IQ/DQ scores do benefit from epilepsy surgery even though their chance to achieve

397 seizure freedom decreases with lower IQ/DQ scores (Malmgren et al. 2008). Overall, our data

398 support the original concept of epileptic encephalopathy wherein epileptic activity itself

399 contributes to cognitive decline (Berg et al. 2010). Therefore, in light of our findings supported

400 by multiple studies advocating for epilepsy surgery as a treatment of choice in drug resistant

401 focal epilepsy, we conclude that epilepsy surgery leads to favourable seizure and cognitive

402 outcomes in carefully selected patients (Dwivedi et al. 2017; Harvey et al. 2008; Holthausen et

403 al. 2013; Ryvlin et al. 2014; Van Schooneveld & Braun 2013).

404 To summarize, patients with varying underlying aetiologies tend to differ in their pre- and post-

405 surgical IQ/DQ scores but not in their IQ/DQ change, we therefore suggest that despite the

406 differences in pre-surgical cognitive performance, patients with various underlying aetiologies

407 may all benefit from epilepsy surgery. These findings are also supported by the regression curve

408 equation that shows that patients with lower pre-surgical IQ/DQ tend to profit most from

409 epilepsy surgery. Understandably, they would still achieve significantly lower post-surgical

410 IQ/DQ scores as post-surgical IQ/DQ scores correlate strongly with pre-surgical IQ/DQ.

411   Admittedly, our study displays certain limitations, the greatest being the short follow-up period

412   of one year. Indeed, some authors show that only longitudinal studies over lengthy study periods

413   provide solid evidence of cognitive improvement after epilepsy surgery, associated with

414   cessation of antiepileptic medication (Sibilia et al. 2017; Skirrow et al. 2011). On the other hand,

415   the length of follow-up period in previously published studies spans from few months to many

416   years (Moosa & Wyllie 2017; Van Schooneveld & Braun 2013). Most recently published studies

417   do provide evidence of cognitive improvement or improved cognitive trajectory over longer time

418   periods; however, these studies have other limitations, e.g. smaller sample size or they fail to

419   discern between different aetiologies (Puka et al. 2017; Sibilia et al. 2017). Most importantly

420   however, in our study, we aimed primarily to compare trends in cognitive performance between

421   the periods of developing vs. established epilepsy surgery centre and to analyse whether epilepsy

422   surgery candidates differ in their cognitive performance based on underlying aetiology and

423   epileptic syndrome. Further longitudinal studies are needed to provide unequivocal evidence that

424   paediatric epilepsy surgery can reverse the course of epileptic encephalopathy and lead to

425   cognitive recovery or at least prevent further cognitive decline.

426   Due to repeated neuropsychological testing, we could not have completely eliminated a possible

427   effect of repeated testing. Although some authors claim that the practice effect in paediatric

428   population is not significant (Westerveld et al. 2000), others believe it may interfere with the

429   correct evaluation of cognitive outcomes in paediatric epilepsy surgery (Sherman et al. 2003). In

430   addition, given the age diversity of our population, our study faced the issue of comparability of

431   various age-adjusted versions of IQ/DQ tests. We believe both of these issued will be addressed

432   in future studies in which we aim to validate our findings over a longer follow-up period with

433   wider intervals between repeated testing on a more homogenous age-groups of children.

434   Despite rather large sample size, some numbers of patients in individual subgroups remain small

435   and this precluded some further analyses, e.g. the effect of complications of epilepsy surgery on

436   post-surgical IQ/DQ score. However this also shows that overall, major complications of

437   epilepsy surgery occur rarely in our centre as well as others (Bjellvi et al. 2015). Our study also

438   lacked data on socioeconomic status of patients' families that might have affected IQ/DQ

439   change; in fact, parents' education seems to independently contribute to IQ/DQ increase after

440   epilepsy surgery (Meekes et al. 2015), while income and residence do not have significant effect

441   (Puka et al. 2016). Therefore, the effect of families' socioeconomic status on cognitive

442   performance in children undergoing epilepsy surgery warrants further consideration, both in

443   research and in clinical practice.

444   Another significant limitation concerns the effect of antiepileptic drugs (AED) on post-surgical

445   cognitive outcome. It has been shown that AED withdrawal leads to improved cognitive skills in

446   children undergoing epilepsy surgery, and that IQ scores tend to increase with decreasing

447   number of AED (Boshuisen et al. 2015b). Given the short period of post-operative follow-up

448   period we were unable to assess the effect of AED withdrawal as the vast majority of patients

449   remain on pre-surgical dose of AED at least one year after epilepsy surgery. Accumulating

450   evidence advocates for early AED withdrawal (Boshuisen et al. 2012; Braun & Schmidt 2014),

451   and a randomized control trial on the effect of early vs. late AED withdrawal on cognitive

452   outcomes is ongoing (Boshuisen et al. 2015a).

453

454   **Conclusion**

455   Epilepsy surgery may lead to improvement of cognitive performance in patients with drug

456   resistant focal epilepsy, especially in those with lower pre-surgical IQ/DQ scores; this warrants

457 early referral to epilepsy surgery centres. Patients with varying aetiologies and epileptic

458 syndromes enter epilepsy surgery evaluation with distinct cognitive performances and diverse

459 potential for recovery and should be counselled accordingly. In future, longitudinal studies with

460 lengthier follow-up periods and inclusion of novel genetic findings may elucidate mechanisms

461 behind cognitive dysfunction in patients with focal drug resistant epilepsy and contribute to more

462 precise prognosis and counselling.

463

464 **Acknowledgements**

465 The authors would like to thank their respective clinical teams taking care of patients involved

466 and to the patients and their families themselves for their support and collaboration on the study.

467
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Figure 1

Result of the regression analysis.

The figure depicts correlation of pre- and post-surgical IQ/DQ scores, along with the respective confidence intervals (dashed line) in the whole dataset, in children above and below 6 and 12 years of age. The respective regression equations are listed too.

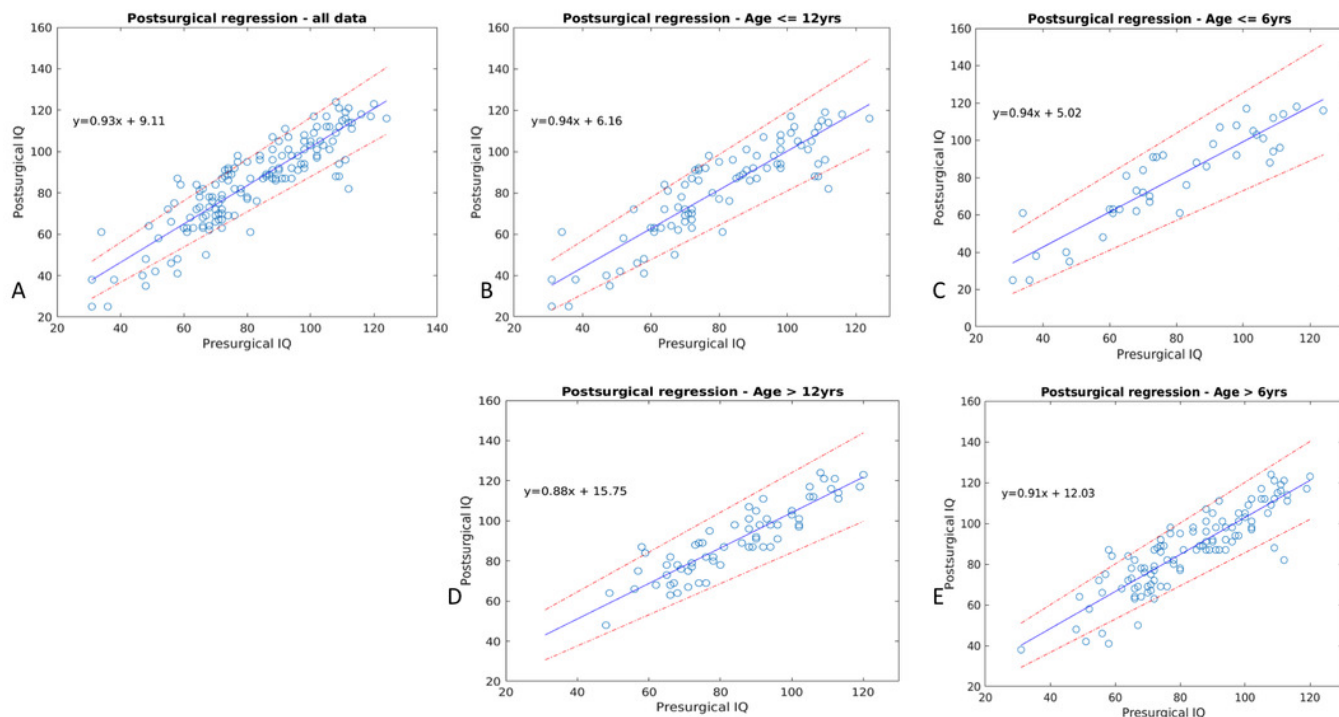
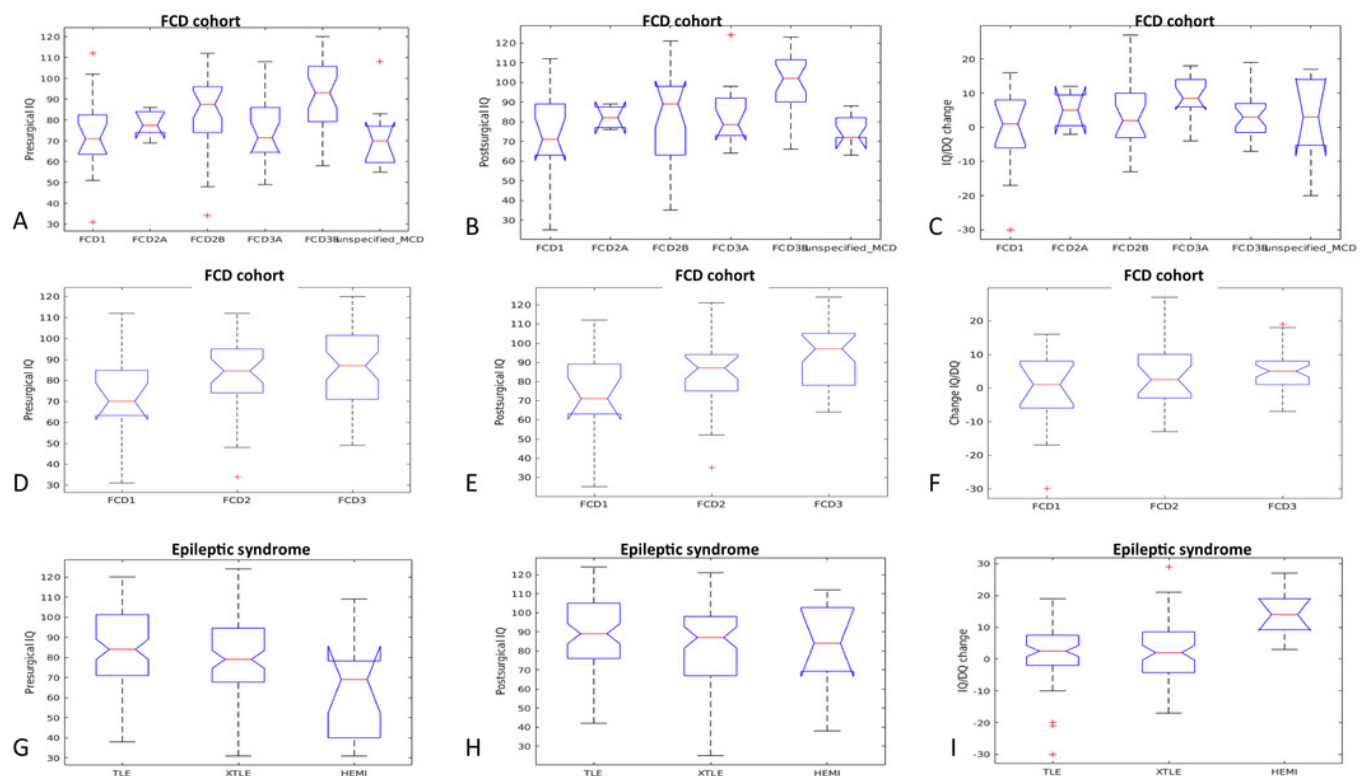



Figure 2

Pre-and post-surgical IQ-DQ and IQ/DQ change in distinct groups of patients according to epilepsy-related features.

FCD: focal cortical dysplasia, MCD: malformations of cortical development, TSC: tuberous sclerosis complex, TLE: temporal lobe epilepsy, XTLE: extratemporal lobe epilepsy, HEMI: hemispheric epilepsy.

Demographic features of patients included in the study.

The table shows demographic features of patients included in the study. TLE: temporal lobe epilepsy, XTLE: extratemporal lobe epilepsy, HEMI: hemispheric epilepsy, FCD: focal cortical dysplasia, MCD: malformations of cortical development, TSC: tuberous sclerosis complex, FBTCS: focal to bilateral tonic clonic seizure, LEAT: long-term epilepsy-associated tumours

	pre-2011 [count]	pre-2011 [%]	post-2011 [count]	post-2011 [%]	overall [count]	overall [%]
sex						
female	40	51.3	60	48.0	100	49.3
male	38	48.7	65	52.0	103	50.7
family history of epilepsy	10	12.8	20	16.0	30	14.8
prenatal risks	11	14.1	16	12.8	27	13.3
febrile seizures	12	15.4	5	4.0	17	8.4
trauma	4	5.1	1	0.8	5	2.5
inflammation	3	3.9	3	2.4	6	3.0
infantile spasms	5	6.4	15	12.0	20	9.9
epileptic syndrome						
temporal lobe epilepsy	39	50.0	54	43.2	93	45.8
extratemporal epilepsy	37	47.4	57	45.6	94	46.3
hemispheric epilepsy	2	2.6	14	11.2	16	7.9
seizure frequency						
daily	47	60.3	83	66.4	130	64.0
less than monthly	19	24.4	10	8.0	29	14.3
monthly	7	9.0	8	6.4	15	7.4
weekly	5	6.4	24	19.2	29	14.3
status epilepticus	11	14.1	14	11.2	25	12.3
focal to bilateral tonic clonic seizures	39	50.0	47	37.6	86	42.4
abnormal neurological finding	28	35.9	33	26.4	61	30.1
MRI finding						
lesional	73	93.6	122	97.6	195	96.1
non-lesional	5	6.4	3	2.4	8	3.9
surgery type						
extended lesionectomy	16	20.5	20	16.0	36	17.7
hemispherectomy/hemispherotomy	2	2.6	15	12.0	17	8.4

tailored resection	32	41.0	47	37.6	79	38.9
lesionectomy	7	9.0	14	11.2	21	10.3
standardized resection	21	26.9	29	23.2	50	24.6
surgery extent						
focal resection	24	30.8	57	45.6	81	39.9
hemispherectomy/hemispherotomy	2	2.6	11	8.8	13	6.4
multilobar resection	12	15.4	13	10.4	25	12.3
unilobar resection	40	51.3	44	35.2	84	41.4
surgery localization						
left hemisphere	39	50.0	66	52.8	105	51.7
midline	1	1.3	6	4.8	7	3.5
rigt hemisphere	38	48.7	53	42.4	91	44.8
complete resection	59	75.6	105	84.0	164	80.8
histopathology						
encephalitis	1	1.3	3	2.4	4	2.0
hippocampal sclerosis	20	26.0	12	9.8	32	16.0
glial scar	6	7.8	6	4.9	12	6.0
MCD	24	31.2	36	29.3	60	30.0
tuberous sclerosis complex	6	7.8	12	9.8	18	9.0
vascular lesion	0	0.0	3	2.4	3	1.5
hypothalamic hamartoma	1	1.3	6	4.9	7	3.5
normal	0	0.0	4	3.3	4	2.0
tumour	19	24.7	41	33.3	60	30.0
not available					3	
FCD class						
FCD1	7	14.6	8	11.9	15	13.0
FCD2A	0	0.0	6	9.0	6	5.2
FCD2B	15	31.3	14	20.9	29	25.2
FCD3A	11	22.9	10	14.9	21	18.3
FCD3B	13	27.1	21	31.3	34	29.6
unspecified_MCD	2	4.2	8	11.9	10	8.7

early post-operative seizures	8	10.4	17	13.6	25	12.4
complication type						
major	4	40.0	6	37.5	10	38.5
minor	6	60.0	10	62.5	16	61.5
FCD simplified classification						
FCD1	7	15.2	8	13.6	15	14.3
FCD2	15	32.6	20	33.9	35	33.3
FCD3	24	52.2	31	52.5	55	52.4
epoch						
before 2011	78	100.0	0	0.0	78	38.4
after 2011	0	0.0	125	100.0	125	61.6
1 year follow-up period						
seizure-free	66	86.8	106	89.8	172	88.7
seizure reduction<50%	6	7.9	6	5.1	12	6.2
seizure reduction ≥50%	0	0.0	2	1.7	2	1.0
seizure reduction ≥90%	4	5.3	4	3.4	8	4.1
not available					9	

Table showing results of univariate testing of categorical variables.

The table shows categorical variables associated with pre- (A) and post-surgical IQ/DQ (B) and IQ/DQ change (C). CI: confidence interval, SE: standard error, SD: standard deviation, FCD: focal cortical dysplasia, df: degrees of freedom

A: Determinants of pre-surgical IQ/DQ (n=191)						
variable name	median difference (95% CI)	mean difference (95% CI)	p-value	effect size	Fstat	df
prenatal risks	8 (0,17)	9.0(1,17)	0,031	0,019	4,722	189
infantile spasms	20 (9,30)	19.1(10,28)	<0.001	0,070	15,305	189
epileptic syndrome			0,001	0,058	6,832	188
seizure frequency			0,035	0,029	2,921	187
status epilepticus	11 (2,20)	10.7(2,19)	0,018	0,024	5,725	189
abnormal neurological finding	18 (13,25)	18.5(13,24)	<0.001	0,171	40,231	189
histopathology			<0.001	0,184	6,281	189
FCD class			0,001	0,145	4,573	189
B: Determinants of post-surgical IQ/DQ (n=156)						
variable name	median difference (95% CI)	mean difference (95% CI)	p-value	effect size	Fstat	df
infantile spasms	26 (13,39)	25.6(15,36)	<0.001	0,121	22,383	154
seizure frequency			0,014	0,048	3,631	152
status epilepticus	15 (5,25)	14.8(4,26)	0,010	0,036	6,855	154
abnormal neurological finding	17 (9,25)	16.6(10,23)	<0.001	0,119	21,928	154
surgery type			<0.001	0,109	5,724	151
surgery extent			<0.001	0,118	7,902	152
complete resection	-14(-21,-6)	-13.3(-21,-6)	0,001	0,062	11,268	154
histopathology			<0.001	0,243	7,129	145
FCD class			0,001	0,177	4,572	78
FCD1			0,008	0,072	7,443	82
FCD3B			<0.001	0,178	19,009	82
1 year follow-up period			0,035	0,037	2,953	150
age class12	-6(-12,0)	-7.5(-14,-1)	0,027	0,025	4,956	154
age class6	-7(-16,0)	-8.7(-16,-2)	0,024	0,026	5,167	154
C: Determinants of IQ/DQ change (n=154)						
variable name	median difference (95% CI)	mean difference (95% CI)	p-value	effect size	Fstat	df
epileptic syndrome			0,002	0,069	6,635	151
surgery type			0,025	0,046	2,863	149
surgery extent			0,011	0,052	3,822	150
FCD1			0,047	0,037	4,080	80
FCD3A			0,022	0,052	5,430	80
age class12	-4(-7,-2)	-4.6(-7,-2)	0,004	0,048	8,795	152
age class6	-4(-8,-1)	-4.0(-7,-1)	0,027	0,025	4,961	152

Table showing results of univariate testing of continuous variables.

The table shows continuous variables associated with pre- (A) and post-surgical IQ/DQ (B) and IQ/DQ change (C). SE: standard error, dfe: degrees of freedom for error, sse: sum of squares for error, dfr: degrees of freedom for regression, ssr: sum of squares for regression

A: Determinants of presurgical IQ/DQ (n=191)			
Univariate Regression			
Variable	**age of first seizure**		
intercept	73.9		
SE	2		
t statistics	36.88		
p value	<0.001		
beta 1	1.55		
SE	0.3		
t statistics	5.2		
p value	<0.001		
dfe	189		
sse	65805		
dfr	1		
ssr	9416		
f	27.05		
p value	<0.001		
r2 effect size	0.13		
B: Determinants of postsurgical IQ/DQ (n=156)			
Univariate Regression			
Variable	**age of first seizure**	**age at surgery**	**duration of epilepsy**
intercept	75.6	77.87	90
SE	2.3	3.56	2.65
t statistics	33.05	21.86	33.9
p value	<0.001	<0.001	<0.001
beta 1	1.99	0.7	0.8

SE	0.35	0.3	0.36
t statistics	5.78	2.38	-2.3
p value	<0.001	0.02	0.02
dfe	154	154	154
sse	57589	67579	67798
dfr	1	1	1
ssr	12474	2484	2264
f	33.36	5.66	5.14
p value	<0.001	0.02	0.02
r2 effect size	0.18	0.04	0.03

C: Determinants of IQ/DQ change (n=154)

Univariate Regression

Variable	age at surgery	duration of epilepsy
intercept	-0.4	2.19
SE	1.66	1.25
t statistics	-0.24	1.75
p value	0.81	0.08
beta 1	0.36	0.21
SE	0.14	0.17
t statistics	2.58	1.23
p value	0.01	0.22
dfe	152	152
sse	14157	14629
dfr	1	1
ssr	617.55	145.83
f	6.63	2

p value	0.01	0.22	
r2 effect size	0.04	0.01	

Table showing results of multivariate testing.

The table shows the results and features of multiple regression based on the general linear model of pre-(A), post-surgical IQ/DQ (B) and IQ/DQ change (C). SE: standard error; TLE: temporal lobe epilepsy, XTLE: extratemporal lobe epilepsy, HEMI: hemispheric epilepsy, FCD: focal cortical dysplasia, MCD: malformations of cortical development, TSC: tuberous sclerosis complex, FBTCS: focal to bilateral tonic clonic seizure, LEAT: long-term epilepsy-associated tumours.

A: Multiple regression based on the general linear model of pre-surgical IQ/DQ				
Variable	**Estimate**	**SE**	**t statistics**	**p value**
Intercept	71.61	4.84	14.81	<0.001
age at first seizure	0.82	0.38	2.18	0.03
abnormal neurological finding	-20.08	5.03	-3.99	<0.001
FCD IIa	6.95	7.33	0.95	0.35
FCD IIb	14.29	4.97	2.87	5
FCD IIIa	1.02	5.21	0.2	0.84
FCD IIIb	14.72	4.79	3.07	3
unspecified MCD	12.75	6.82	1.87	0.06
Model Characteristics	**Value**			
observations	106			
error degrees of freedom	97			
estimated dispersion	221			
F-statistic vs. constant model	7.77			
p value	<0.001			
r2 effect size	0.32			
B: Multiple regression based on the general linear model of post-surgical IQ/DQ				
Variable	**Estimate**	**SE**	**t statistics**	**p value**
Intercept	93.6	11.55	8.1	<0.001
age at first seizure	0.82	0.34	2.42	0.02
status epilepticus	-11.27	4.76	-2.37	0.02
hemispherectomy/hemispherotomy	-12.59	7.74	-1.63	0.11
multilobar resection	-18.41	4.63	-3.98	<0.001
unilobar resection	-9.06	3.51	-2.58	0.01
complete resection	9.34	3.76	2.48	0.01

	Estimate	SE	t statistics	p value
hippocampal sclerosis	-9.61	11.35	-0.85	0.4
glial scar	-10.65	11.64	-0.92	0.36
MCD	-16.69	10.68	-1.56	0.12
TSC	-30.83	11.38	-2.71	0.01
vascular lesion	4.03	15.83	0.25	0.8
hypothalamic hamartoma	-13.37	12.88	-1.04	0.3
normal histopathology	-14.47	14.44	-1	0.32
tumour	-2.07	10.84	-0.19	0.85
Model Characteristics	value			
observations	154			
error degrees of freedom	139			
estimated dispersion	268			
F-statistic vs. constant model	8.54			
p value	<0.001			
r2 effect size	0.46			
C: Multiple regression based on the general linear model of IQ/DQ change				
Variable	**Estimate**	**SE**	**t statistics**	**p value**
intercept	10.91	3.28	3.33	1
TLE	-13.53	3.3	-4.09	<0.001
XTLE	-12.38	3.26	-3.8	<0.001
age at surgery	0.44	0.14	3.18	2
Model Characteristics	value			
observations	154			
error degrees of freedom	150			
estimated dispersion	84.8			
F-statistic vs. constant model	8.07			

p value	<0.001			
r2 effect size	0.14			

Summary of post-hoc tests.

(A) Post-hoc tests for variables associated with presurgical IQ/DQ. (B) Post-hoc tests for variables associated with postsurgical IQ/DQ. FCD: focal cortical dysplasia, MCD: malformations of cortical development, TSC: tuberous sclerosis complex, HS: hippocampal sclerosis, df:degrees of freedom

A: Post-hoc tests for IQ/DQ_presurgical

variable name	mean difference	median difference	p-value	effect size	Fstat	df
glial scar_tumour	-22.79 (-41.92,-3.67)	-20(-36,-8)	<0.001	0.189	16.583	66
MCD_tumour	-13.84 (-24.72,-2.97)	-14(-20,-7)	<0.001	0.130	17.613	110
TSC_tumour	-29.23 (-45.28, -29.23)	-31(-39,-21)	<0.001	0.355	41.261	72
HS_tumour	-12.86 (-25.82, -12.86)	-14(-22,-5)	0.001	0.109	11.683	86
FCD1_FCD3B	-19.46 (-35.02, -3.89)	-22(-33,-8)	0.001	0.208	12.815	44
FCD3A_FCD3B	-17.70 (-32.20,-3.19)	-19(-28,-9)	<0.001	0.220	15.088	49
FCD3B_unspecified MCD	20.42 (1.28,39.57)	21(5,34)	0.006	0.168	8.664	37
TLE_hemi	20.95 (7.09,34.80)	21(36,7)	0.001	0.104	12.709	100
XTLE_hemi	16.69 (2.84,30.54)	18(32,3)	0.005	0.066	8.175	100

B: Post-hoc tests for IQ/DQ_postsurgical

variable name	mean difference	median difference	p-value	effect size	Fstat	df
MCD_tumour	-20.69 (-33.36,-8.02)	-21(-27,-14)	<0.001	0.241	28.870	87
TSC_tumour	-35.71 (-53.29,-18.12)	-35(-47,-24)	<0.001	0.457	49.766	57
HS_TSC	22.33 (3.10,41.55)	21(8,35)	0.001	0.221	12.379	39
hamartoma_tumour	-23.25 (-45.26,-1.24)	-19(-36,-3)	0.005	0.136	8.722	48
FCD1_FCD3B	-26.55 (-44.98,-8.13)	-27(-41,-12)	<0.001	0.307	17.353	36
FCD3A_FCD3B	-20.61 (-35.34,-5.89)	-20(-29,-7)	0.005	0.180	9.133	36
unspecified MCD_FCD3B	23.84 (0.31,47.37)	26(13,36)	0.002	0.275	12.005	28