

(1) Title of manuscript:

**Title: Determinants of IQ outcome after focal epilepsy surgery in childhood: a longitudinal case-control neuroimaging study**

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## Summary

### *Objective :*

IQ outcomes after paediatric epilepsy surgery show significant individual variation. Clinical factors such as seizure cessation or antiepileptic medication discontinuation have been implicated, but do not fully account for the heterogeneity seen. Less is known about the impact of neurobiological factors, such as brain development and resection location. This study examines clinical and neuroimaging factors associated with cognitive outcome after epilepsy surgery in childhood.

### *Methods:*

Fifty-two children (28 boys, 24 girls) were evaluated for epilepsy surgery and re-assessed on average 7.7 years later. In the intervening time 13 were treated pharmacologically and 39 underwent focal surgery (17 temporal, 16 extratemporal, 6 multilobar; mean age at surgery 14.0 years). Pre- and post-surgical assessments included IQ tests and T1-weighted brain images. Predictors of IQ change were investigated, including voxel-based analyses of resection location, and grey and white matter volume change.

### *Results:*

Overall modest IQ improvement was seen in children treated surgically, but not in those treated pharmacologically only. Applying a  $\geq 10$  point change threshold, 39% of the surgically-treated children improved, whilst 10% declined. Clinical factors associated with IQ increases were lower preoperative IQ and longer follow-up duration, while seizure and antiepileptic medication cessation were not predictive. Among neuroimaging factors we observed that left anterior temporal resections impacted negatively on verbal reasoning, linked to full scale IQ decline. In contrast, grey matter volume change in ipsi- and contralesional hemispheres were positively correlated with IQ change. Voxel-based morphometry identified the grey matter volume change in the contralesional dorsolateral frontal cortex as most strongly associated with IQ improvement.

### *Significance:*

We show that a variety of factors are likely to contribute to patterns of post-surgical change in IQ. Neuroimaging results indicate that left anterior temporal resections constrain development of verbal cognition, whilst simultaneously cortical growth after surgical

treatment can support improvements in IQ.

**Key words**

Seizures, IQ, outcomes, neurosurgery, neuroimaging, longitudinal

**Key point box**

- Children with temporal and extratemporal surgery for epilepsy overall show modestly improved IQ at 2-16 years post-surgery
- However, there is significant individual variation of IQ outcomes after paediatric epilepsy surgery
- Post-surgical grey matter growth is associated with IQ improvements
- Left anterior resections may constrain the development of verbal cognition

## Introduction

Resective surgery is a treatment for severe, medication-resistant epilepsy which aims to cure seizures by localizing and safely removing a critical mass of the epileptogenic network in the brain.<sup>1</sup> Around 60% of children are free from seizures at five or more years after temporal or extratemporal surgery.<sup>2</sup> Research indicates that in children epilepsy surgery overall has either little impact,<sup>3-7</sup> or possibly a positive effect<sup>8-12</sup> on cognitive function, as measured by intelligence quotient (IQ). However, embedded in these group effects is significant inter-individual variation. Recent systematic reviews of studies reporting IQ outcomes after temporal and extra-temporal lobe surgery found that 21-30% of patients improved, 58-67% remained stable, and 10-12% deteriorated.<sup>13,14</sup> This begs the question: why do some children show improvement but others decline?

Factors that are likely to contribute include post-surgical seizure freedom,<sup>3,8</sup> cessation of antiepileptic drug (AED) use,<sup>4,9,15</sup> preoperative IQ,<sup>8,9,16</sup> and duration of follow-up.<sup>8,9</sup> Less attention has been paid to how brain structural changes and post-surgical brain development are linked to cognitive function. Epilepsy and refractory seizures are associated with reductions in brain volume,<sup>17,18</sup> as well as abnormal structural brain development.<sup>19</sup> These findings may indicate seizure-induced brain growth suppression or bilaterally acquired cortical damage caused by seizures.<sup>18</sup> How these effects are modified by surgery requires investigation.

One study that has evaluated this association found improved Full-Scale IQ (FSIQ) after childhood temporal lobe surgery with concurrent change in global brain grey matter volumes, with greater improvements associated with more positive volumetric changes.<sup>9</sup> In this same sample, better semantic memory outcome was associated with greater post-surgical temporal pole integrity.<sup>20</sup> Surgery may therefore simultaneously constrain and enhance cognitive development.

The current study follows a longitudinal case-control design, examining IQ change after childhood temporal and extratemporal surgery, compared to an epilepsy control group with similar clinical characteristics. We aim to identify factors associated with change in IQ. We expect to find post-surgical IQ increase in the surgically treated sample, and will examine the role of the following predictors of post-surgical cognitive change: (1) clinical contributors (such as epilepsy and medication factors); (3) side and location of surgery; and (4) brain

growth. Further exploratory analyses attempted to localize brain volume changes associated with IQ change, and identify the most robust predictors of post-surgical IQ change.

## **Methods**

### *Participants*

Children with epilepsy who underwent pre-surgical cognitive evaluation between 1999-2013 in the neuropsychology department of Great Ormond Street Hospital for Children (GOSH) were identified from hospital notes. Children with focal epilepsy and surgery, and children with a history of medication resistant epilepsy who had not undergone surgical treatment were recruited into the study. Participants were selected on the basis that they were able to take part in MR imaging and cognitive assessments. Inclusion criteria: medication-resistant epilepsy (inadequate seizure control after treatment with  $\geq 2$  AEDs), pre-operative IQ assessments available at age  $\geq 5$ , and either focal resective surgery at GOSH or the National Hospital of Neurology and Neurosurgery (NHNN), or continued treatment with antiepileptic drugs. Exclusion criteria: non-fluent in English, hemispherectomy/hemispherotomy, multiple lesionectomies or disconnections, neural implant precluding MRI imaging (shunt or vagus nerve stimulation device) and acquired head injury after surgery. Hospital records identified 61% as having undergone surgery, 30.5% as being treated non-surgically, and 8.5% without clear documentation regarding surgical status.

183 children were considered for inclusion in the study. Of these 33 had undergone non-focal surgical procedures (19 hemispherectomy, 3 disconnections, 3 shunt, 8 vagus nerve stimulator) and were excluded. Six additional patients were excluded due to inability to administer Wechsler IQ assessments at baseline or follow-up (3 at age $<5$  at pre-surgical assessment, 2 non-fluent in English, 1 deaf).

Of 144 remaining children meeting above criteria, two were deceased at follow-up, and 43 were non-contactable. Of the remaining ninety-nine individuals who were contacted, 32 chose not to participate and 14 were unable to take part (pregnant (n=2), disability (n=10) or having moved overseas (n=2)). One participant dropped out before completing IQ assessments at follow-up. Fifty-two participants were recruited: 39 who underwent focal resection, and 13 treated with medication only.

The London Queen Square Ethics Committee approved this study. Consent was obtained from participants aged  $\geq 16$  years at the time of follow-up evaluation. Assent from participants and consent from parents was obtained from those under age 16.

#### *Procedures*

Pre-surgical assessments included MRI imaging, ictal and interictal EEG, and neuropsychological assessment. Age-appropriate IQ assessments were completed using the Wechsler intelligence scales, including Wechsler Scales for Preschool and Primary school age children (WPPSI-II, WPPSI-R), Wechsler Intelligence Scales for Children (WISC-III, WISC-IV), Wechsler Adult Intelligence Scales (WAIS-III, WAIS-IV), and Wechsler Abbreviated Scale of Intelligence (WASI). Baseline refers to the assessment carried out prior to surgery. In those who underwent repeat surgery (n=4), baseline preceded the first surgery. For non-surgical patients baseline refers to their first assessment at GOSH.

Baseline full-scale IQ (FSIQ) data were available in all patients. Component scaled scores included: verbal comprehension index (VCI, available in n=48), processing speed index (PSI, n=44), related indices for perceptual reasoning and perceptual organization (PRI/POI, n=48), and related indices for working memory and freedom from distractibility (WMI/FFDI, n=45). Incomplete baseline data were due to preschool and abbreviated tests not providing subscale data (n=4), or insufficient subtests completed (n=4). Supplementary pre- or post-operative IQ data were available in 70% (n=38), most frequently at 1 year follow-up (total number of IQ assessments available =161).

Follow-up assessment was completed from June 2012-April 2016, including IQ assessment and structural MRI. Surgical cases and controls were recruited concurrently. Follow-up was on average 7.2 years after surgery (range 1.6-15.7), and 7.7 years after baseline assessment (range 2.5-16). Age-appropriate IQ tests were carried out (WISC-IV for age  $\leq 16$  years and two months, WAIS-IV for all others).

Volumetric preoperative MRI scans were available for 37 focal surgery and 12 non-surgical patients (94.2% of total sample). MRI scans were obtained from all participants at follow-up. All MRI scans acquired prior to 2007 (n=20, 41% of scans at baseline, primarily in the surgical sample (n=19)) were obtained on a 1.5 T Siemens Vision System (Siemens, Erlangen, Germany) and included a volume T1-weighted scan using a 3-dimensional magnetization-prepared rapid gradient echo sequence (repetition time 10 ms; echo time 4 ms; flip angle

12°; voxel size 1.0x1.0x1.25 mm). Scans acquired after 2007, including all follow-up scans, were obtained on a 1.5 T Siemens Avanto System. Three-dimensional volume T1-weighted scans were acquired using a 3DFLASH sequence (repetition time 11 ms; echo time 5 ms; flip angle 15°, voxel size 1.0x1.0x1.0 mm).

#### *MRI analysis*

Radiological diagnoses were given by experienced paediatric neuroradiologists, who evaluated all pre-operative MRI images. Locations of resections or lesions were categorized by the research team as follows: frontal-central, parietal, occipital, temporal, or multilobar abnormalities/resections. Resections were manually traced in native space on post-operative T1-weighted MRI images, to provide resection maps and derive resection volumes. Tracings were completed with reference to the contra-lesional hemisphere using MRICron ([www.mccauslandcenter.sc.edu/crnl/mricron/](http://www.mccauslandcenter.sc.edu/crnl/mricron/)) by one researcher (CS).

Resection maps were normalized to the ICBM space template in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), and entered into voxel-based lesion symptom mapping analysis (VLSM)<sup>21</sup> using NPM (<https://www.mccauslandcenter.sc.edu/crnl/tools>)<sup>22</sup>. Voxel-wise T-tests evaluated resections associated with change in IQ (postoperative – preoperative IQ score) in regions of the brain resected in  $\geq 2$  individuals. The level of significance was set at  $\leq 0.05$  with false discovery rate (FDR) correction for multiple comparisons.

Images were segmented into white matter (WM), grey matter (GM) and CSF using the Computational Anatomy Toolbox 12 (CAT12; <http://dbm.neuro.uni-jena.de/cat/>) for SPM12, and normalized into ICBM space. This segmentation procedure estimates tissue probabilities without priors and uses a partial volume segmentation approach to estimate the amount of each tissue type in each voxel. Quality estimates are provided for each scan, and one baseline scan (<65% quality) was excluded from analyses. GM and WM volumes were extracted for ipsi-lesional and contra-lesional hemispheres. Summation of GM, WM and CSF volumes provided total intracranial volume (TIV).

Maps of brain volume change were obtained by subtracting normalised pre-operative GM and WM segmented images from those obtained at follow-up using the `imcalc` function in SPM12. Images were smoothed using a 10-mm full-width half-maximum Gaussian kernel. Voxel-wise regression examined FSIQ change in relation to contra-lesional GM and WM

volume changes, covarying for TIV change, sex and age at follow-up. A voxel-wise threshold of  $p < 0.05$  with family-wise error correction (FWE) was used for the entire contra-lesional hemisphere for right and left surgery groups separately. Regions of interest implicated in IQ included the following contra-lesional brain structures: dorsolateral prefrontal cortex (Brodmann areas (BA) 6, 9, 10, 45, 46, 47), inferior (BAs 39,40) and superior (BA 7) parietal lobule, the anterior cingulate (BA 32) and temporal (BAs 21,37) and occipital regions (BAs 18, 19).<sup>23</sup> These regions were evaluated at a  $p < 0.001$  uncorrected threshold with cluster size of  $\geq 200$ .

#### *Statistical analysis*

Change indices were calculated by subtracting baseline from follow-up values (positive values index increases, negative values index decrements). Clinical and brain structural factors associated with post-surgical outcome were examined in the surgical cohort only. Analyses were completed in SPSS version 24 and SAS 9.4.

All data were assessed for normality using the Shapiro-Wilk statistic, followed by parametric and non-parametric tests, as appropriate. Frequencies are reported with 95% confidence intervals, derived from bootstrapping with simple sampling in 1000 samples, presented in square brackets.

A threshold of gains or losses of 10 FSIQ points was applied to examine individual change, in line with previous research,<sup>8,13,24,25</sup> and in keeping with broadly applied ranges for categorizing cognitive ability.<sup>26</sup>

Group-level analysis examined differences in epilepsy-related and clinical characteristics (seizure onset, duration of epilepsy, seizure frequency, medication cessation, baseline IQ, duration of follow-up) between surgical and non-surgical groups. Furthermore, in the surgical group the effect of clinical characteristics was examined on FSIQ at baseline, follow-up and change over time. Analyses were completed with t-tests, Mann-Whitney U-tests, analysis of variance (ANOVA), Kruskal Wallis, Wilcoxon Signed Rank test, chi-square and Fisher's exact tests, bivariate and partial correlations, as required.

Longitudinal analyses comparing pre-to post-operative FSIQ change between surgical and non-surgical groups were conducted with repeated-measures ANOVA. These analyses were



repeated as an Analysis of Covariance after including as covariates demographic measures that differed, or showed a trending difference between groups at baseline. Change in individual component scaled scores over time were examined with a 2x2x4 repeated measures ANOVA, with independent predictors including group (surgical, non-surgical), time (baseline, follow-up), and component scaled scores (VCI, PRI/POI, WMI/FFDI and PSI). Departures from sphericity were examined, and Greenhouse-Geisser corrections were adopted where required.

To examine longitudinal change over all available FSIQ data, including supplementary pre- and post-operative assessments, a linear mixed model with random intercept and restricted (residual) maximum likelihood estimation procedure was carried out in SAS software package. This allowed test results to account for correlated observations nested within individuals. FSIQ was entered as dependent variable, and independent variables included surgical status at time of assessment (did not (yet) undergo surgical treatment vs. treated surgically), duration of time from baseline (time), and time\*surgical status interaction. Test type (child vs. adult test) was included as an independent predictor since transition from child to adult assessments can impact on IQ scores.<sup>17</sup>

To identify the most robust predictors of FSIQ change after surgery, all clinical and brain imaging measures associated with FSIQ change, including neuroimaging predictors, were included in a multiple linear regression using the Enter method. Predictors were entered in order of their strength of association with FSIQ change.

## **Results**

### *Participants*

Surgeries were completed at GOSH in 37 individuals (at age  $\leq 18$ ), and at NHNN in two participants (age  $\geq 18$ ) who were recruited into the study (average age at first surgery 14 years, range 6-18). Comparison with a subgroup of participants in whom recruitment was unsuccessful (n=59 where pre-surgical IQ assessments were documented in surgical databases), indicated a significant difference between groups (non-recruited baseline IQ=78.54, recruited baseline IQ=86.93,  $t=2.28$ ,  $p=0.02$ , Hedges'  $g=0.44$ ). There were no differences in age at first assessment ( $p=0.437$ ), sex ( $p=0.475$ ), side of pathology ( $p=0.181$ ),

lobar location of pathology ( $p=0.620$ ) and presence of daily seizures ( $p=0.395$ ) between recruitment groups.

In the non-surgical epilepsy group, two participants were offered surgical treatment but declined. Eleven participants were not offered surgical treatment due to: lack of visible lesion on MRI ( $n=2$ ), lesion proximity to motor cortex ( $n=2$ ), seizure control gained with AEDs ( $n=4$ ) or predicted benefits of surgery outweighed by likely deficits ( $n=3$ ).

Demographic and clinical data are presented in Table 1, alongside test statistics for group differences. Surgical and non-surgical epilepsy groups did not differ with respect to sex, baseline FSIQ or duration of epilepsy to baseline assessments. However, surgical participants had higher baseline seizure frequency and were significantly older than non-surgical participants at both baseline and follow-up. Duration of follow-up from baseline was also longer for surgical patients. Participants were predominantly right-handed. Where available, presurgical fMRI examination of language lateralization using a covert verb generation task and region of interest analysis centered around Broca's area (methods in <sup>27</sup>), indicated predominantly left lateralized language (table 1) in both surgical and non-surgical groups.

### **Table 1 about here**

#### *Seizure outcome and medication*

Surgical participants were more often seizure-free at follow-up (72%; [95% confidence intervals 63%-85%]) compared with non-surgical participants (15% [0%-39%], Fisher exact test,  $p<0.001$ ). More than half (55%) of those experiencing continuing seizures in surgical and non-surgical groups had reduced seizure frequency. Seizure freedom was highest after frontal-central resections (100%), followed by temporal (77%), multilobar (50%), and parietal (43%). Two of four participants who underwent repeat surgery for continuing seizures were seizure free at follow-up. 50% of surgical patients were no longer taking AEDs at follow [35%-69%], compared with 8% in the non-surgical group [0%-23%]; Fisher's exact test:  $p=0.008$ ).

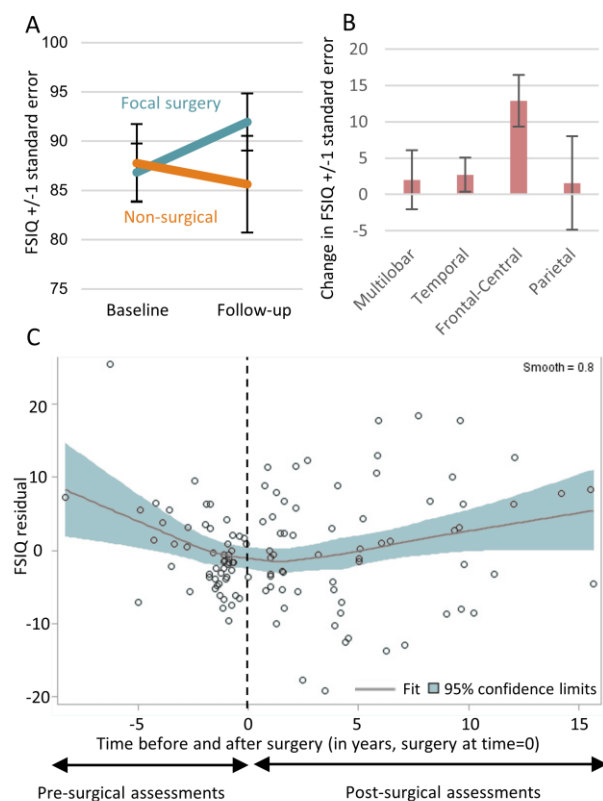
#### *Full Scale IQ and component scaled scores*

FSIQ gains of at least 10 points were observed in fifteen (39% [23%-54%]) surgical patients and one (8% [0%-23%]) non-surgical patient (range 10-28 point change). Losses (range -10 to

-27) were seen in four surgical patients (10% [3%-21%]), and two non-surgical patients (15% [0%-39%]). One participant with decline in FSIQ was psychotic at follow-up and excluded from further analysis of neuropsychological assessments.

Groups showed divergent trajectories between baseline and follow-up, with surgical patients showing modest increases in FSIQ, whilst non-surgical controls showed no overall change (Figure 1A; group-by-time interaction ( $F_{1,49}=5.93$ ,  $p=0.024$ ). Repeating analyses after covarying for group differences at baseline (age at baseline assessment, baseline seizure frequency, and age at first seizure), resulted in a reduced significance level, which failed to meet statistical thresholds ( $F_{1,46}=3.28$ ,  $p=0.08$ ).

Linear mixed modeling of FSIQ over all available assessments showed a reduction of IQ over time (estimate=-1.6, SE=0.51,  $t=-3.11$ ,  $p=0.002$ ), and no main effect of surgical status (estimate=-0.61, SE=1.83,  $t=-0.33$ ,  $p=0.74$ ). However, a significant time by surgical status interaction effect (estimate=0.94, SE=0.31,  $t=3.04$ ,  $p=0.003$ ) was seen, reflecting a changing trajectory of FSIQ over time from before to after surgery. No main effects of child versus adult test type were seen (Estimate=-2.50, SE=1.97,  $t=-1.27$ ,  $p=0.21$ ). Findings in the surgery group were visualized using a locally weighted scatterplot smoothing (LOESS) regression curve of residuals (regressing out baseline FSIQ and test type,  $\alpha=0.05$ , smoothing parameter=80%, Figure 1C), which shows results, where time=0 is centered at time of surgery.



**Figure 1:** IQ change over time. A) Mean FSIQ of surgical and nonsurgical groups from baseline to follow-up, showing interaction of group by time effect. B) Change in FSIQ over period of follow-up (difference post-pre surgery) by resection type. C) Loess graph with fit line, depicting all available FSIQ scores in the surgical group (residuals after regressing out preoperative FSIQ and adult/child test transition) with 95% confidence intervals. Regression line reflects gradual increase in FSIQ from time of surgery (centered at x=0) over time.

Change in IQ component scaled scores (VCI, PRI/POI, WMI/FFDI and PSI) from baseline to follow-up were examined with repeated measures ANOVA. This showed a significant interaction between group and time of assessment (Greenhouse-Geisser corrected  $F_{2,6,41}=6.15$ ,  $p=0.017$ ), but no interaction between group, time of assessment and component scales ( $F_{2,6,41}=1.36$ ,  $p=0.26$ ). Findings reflect the modest overall improvement in IQ scaled scores over time in surgical participants (from mean of 90 to 94.8) in the context of a modest decrease in non-surgical controls (from a mean of 92.3 to 89.4). Changes in FSIQ and component scaled scores were not correlated with the number of IQ assessments completed (range 2-6; rho-range 0.06-0.25,  $p \geq 0.10$ ).

*Clinical factors associated with IQ change after surgery*

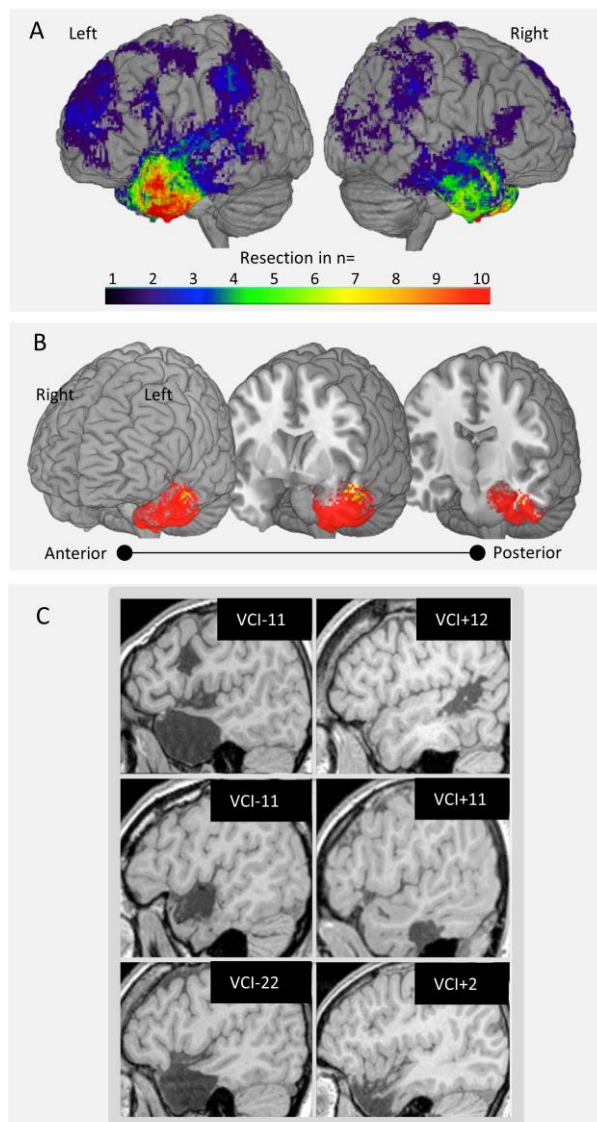
FSIQ change did not differ with respect to the lobar location of resection (Figure 1B:  $F_{3,37}=2.15$ ,  $p=0.11$ ), the side of resection ( $t=-1.80$ ,  $p=0.08$ ), nor the underlying pathology after restriction to the four main pathology types in this sample (dysembryoplastic neuroepithelial tumours, focal cortical dysplasia, mesial temporal sclerosis and cavernoma:  $F_{3,30}=1.65$ ,  $p=0.20$ ).

In surgical participants FSIQ change was inversely correlated with baseline FSIQ ( $r=-0.34$ ,  $p<0.04$ ), with greater increases in those who had lower IQs at baseline. Neither seizure outcomes (seizure free versus continuing seizures:  $F_{1,36}=2.38$ ,  $p=0.13$ ), nor AED discontinuation ( $F_{1,35}=3.19$ ,  $p=0.08$ ) was found to influence IQ change over time. Participants who were seizure free and had discontinued AED treatment at follow-up had higher FSIQ both at baseline and follow-up compared to those with continuing seizures or continued AED treatment (seizure cessation:  $F_{1,36}=13.63$ ,  $p=0.001$ ; AED discontinuation:  $F_{1,35}=5.67$ ,  $p=0.02$ ).

Age at seizure onset was correlated with FSIQ at baseline ( $\rho=0.50$ ,  $p=0.001$ ) and follow-up ( $\rho=0.54$ ,  $p=0.001$ ), but not FSIQ change ( $\rho=0.025$ ,  $p=0.88$ ). Pre-operative epilepsy duration (time between onset and surgery) was inversely correlated with FSIQ at baseline ( $r=-0.48$ ,  $p=0.001$ ) and follow-up ( $r=-0.46$ ,  $p=0.004$ ), but not FSIQ change ( $r=0.05$ ,  $p=0.77$ ). Age at surgery did not correlate significantly with FSIQ at baseline, follow-up, or FSIQ change ( $\rho=-0.01-0.03$ ,  $p\geq 0.84$ ). Longer follow-up was associated with greater IQ improvement ( $\rho=0.38$ ,  $p<0.02$ ).

#### *Brain imaging measures associated with IQ change*

Resection volumes varied in size (1-66 cm<sup>3</sup>) and showed a trending inverse association with FSIQ change ( $\rho=-0.30$ ,  $p=0.07$ ). Voxel-based lesion symptom mapping (VLSM) showed that FSIQ decline was more common after resections to the left superior and middle temporal gyri ( $z=3.67$ ,  $p<0.05$  FDR; Figure 2B). Verbal comprehension index (VCI) reductions were associated with resections to the left temporal pole extending through to the mid temporal lobe including mesial temporal structures ( $z=2.35$ ,  $p<0.05$  FDR; Figure 2B). Three left temporal surgery patients with unchanged or improved VCI, underwent smaller, more posterior or more lateral resections than those cases with VCI declines (Figure 2C). No voxels were associated with change in other component scaled IQ scores (WMI/FFDI, PRI/POI or PSI).



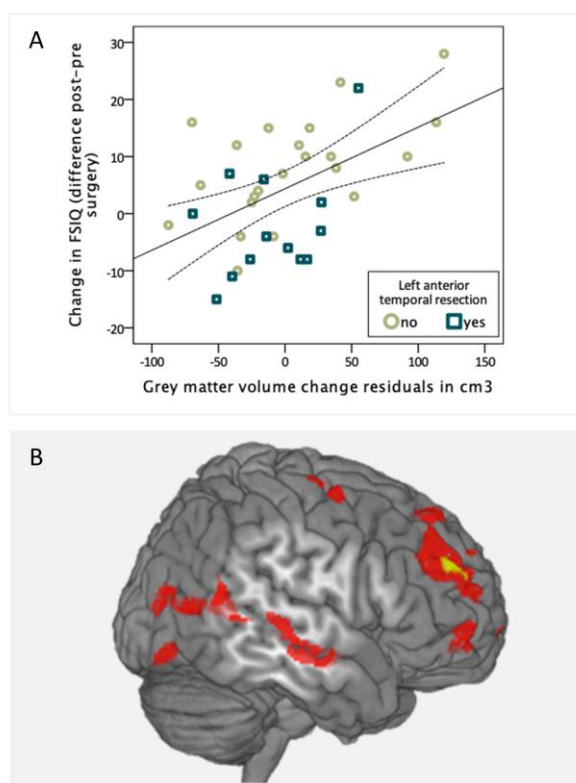
**Figure 2:** A) Resection density map: frequency of resection locations in patients with surgery; B) Results from Voxel-based Lesion Symptom Mapping (VLSM, FDR  $p < 0.05$ ). Highlighted in red: resections associated with declines in VCI; in yellow: resections associated with declines in FSIQ and VCI. C) MRI scans for three patients without VCI decline, and three with largest decline after left temporal surgery.

In the surgery group FSIQ change positively correlated with change in total GM volume ( $r = 0.59$ ,  $p < 0.001$ , Figure 3A), but not WM volume ( $r = -0.09$ ,  $p = 0.61$ ). This correlation remained significant after covarying for transition between MR scanners (partial correlation  $r = 0.61$ ,  $p < 0.001$ ), and was also present when examining separately individuals in whom scanner transition had occurred ( $r = 0.53$ ,  $p = 0.03$ ,  $n = 18$ ) and those where the same MRI

scanner and imaging parameters had been used both at baseline and follow-up ( $r=0.70$ ,  $p=0.002$ ,  $n=17$ ). This correlation remained significant when examining GM volumes in both contra-lesional (controlling for age at follow-up and sex:  $r=0.48$ ,  $p=0.003$ ) and ipsi-lesional hemispheres (additionally covarying for resection volume:  $r=0.55$ ,  $p<0.001$ ).

Change in brain grey matter volume was not associated with seizure cessation ( $t=-0.04$ ,  $p=0.97$ ) nor AED discontinuation ( $t=1.26$ ,  $p=0.22$ ). Examining the variables associated with IQ change in relation to grey matter volume change revealed no significant correlations (baseline IQ:  $r=-0.19$ ,  $p=0.28$ ; duration of follow-up:  $\rho=0.05$ ,  $p=0.79$ ).

Voxel-wise regression analysis identified a peak T-value of 9.1 in the right middle frontal gyrus (MFG; BA 46; coordinates 34,50,26; cluster size 231) in individuals with surgery to the left hemisphere. Here a positive association between GM density change and FSIQ change was seen at  $p=0.003$  (FWE corrected) threshold. Within pre-defined regions of interest, additional clusters in frontal, temporal and occipital lobes emerged (Figure 3B,  $p\leq 0.001$ , uncorrected). No significant contra-lesional volume changes were seen after surgery to the right hemisphere, nor for investigations of contra-lesional WM volume.



**Figure 3:** Grey matter volume change after surgery: A) Changes in total grey matter volume (residuals after regressing out age, sex, duration of epilepsy and resection volume) in relation to FSIQ change in the surgery group, with regression line and 95% confidence intervals of the mean. B) Right hemisphere regions where increase in focal grey matter volume is positively correlated with gain in FSIQ after left hemisphere surgery (yellow  $p < 0.05$  FWE, red  $p < 0.001$  uncorrected).

Parameter estimates for GM change in the contra-lesional MFG cluster were extracted for participants with surgery to left and right hemispheres. These correlated with FSIQ change across both left and right surgical groups ( $r = 0.59$ ,  $p < 0.001$ ), as well as change in perceptual reasoning/perceptual organization indices (PRI/POI:  $r = 0.51$ ,  $p = 0.003$ ), but not with change in other component scaled scores (VCI, WMI/FFDI or PSI:  $r \leq 0.24$ ,  $p \geq 0.20$ ). Associations between FSIQ and PRI/POI change and the parameter estimates were driven primarily by data from individuals with surgery in the left hemisphere. Although these associations were nonsignificant in the right hemispheric focal surgery group, the direction of effect was similar (FSIQ change  $r = 0.38$ ,  $p = 0.20$ ; PRI/POI change  $r = 0.46$ ,  $p = 0.12$ ).

#### *Predictors of IQ change after surgery*

To identify the most robust predictors of FSIQ change after surgery, all clinical and brain imaging measures associated with FSIQ change were compared using multiple linear regression. Predictors were entered in order of their strength of association with FSIQ change: total GM volume change, location of resection (anterior left temporal or elsewhere), time between baseline and follow-up, and preoperative IQ. The regression model was significant ( $F_{4,34} = 8.45$ ,  $p < 0.001$ ,  $R^2 = 0.53$ ), with two significant predictors. GM volume increases predicted a positive IQ change ( $\beta = 0.45$ ,  $p = 0.002$ ), left anterior temporal resections predicted a negative change ( $\beta = -0.38$ ,  $p = 0.01$ ).

#### **Discussion**

Children who underwent focal surgery for epilepsy showed modest group-wise improvement in IQ; this outcome was not observed in a group of children with severe childhood epilepsy who did not undergo epilepsy surgery. However, post-surgical improvement occurred in the context of significant individual variation. Using voxel-based analysis methods we showed that a combination of brain growth and surgical factors may have contributed to IQ change.



Researchers have speculated that eliminating the effects of seizures and AEDs from the developing brain may reduce maturational disturbances in functional cortical networks, playing a critical part in post-surgical improvement.<sup>4</sup> The current research supports this hypothesis and extends previous findings<sup>9</sup> to a much broader group, including children with extratemporal surgery and a variety of pathologies. We find change in IQ to be associated with global grey matter volume changes and localized changes within the contra-lesional prefrontal cortex, an association region maturing later in adolescence,<sup>28,29</sup> and closely implicated in performance on cognitive assessments of IQ.<sup>23</sup>

Overall a reduction in grey matter volume from pre- to post-surgical assessment was seen in 83% of participants who underwent surgery. This likely reflects the resections themselves in combination with maturational decreases in cortical thickness from childhood into adulthood.<sup>30</sup> Research has shown that developmental trajectories in cortical thickness, in frontal regions in particular, vary according to intellectual development of the study subjects.<sup>31</sup> Whilst local cortical thickness and volume shows a primarily linear decline with age during this time period, local cortical surface area shows quadratic growth in a range of brain regions including the prefrontal cortex (increasing until adolescence and then declining).<sup>32</sup> Moreover, our findings are in agreement with research showing that global and local grey matter volume is correlated with IQ.<sup>33,34</sup>

Verbal reasoning declined in children with surgery to the left anterior temporal lobe, a brain region implicated in semantic memory functions in adults.<sup>35</sup> Results indicate reduced reorganizational capacity for semantic functions, broadly in line with results from a previous study showing that better semantic memory is associated with greater temporal pole integrity after paediatric temporal lobe surgery.<sup>20</sup> Further work is now required to examine underpinnings of this decline, to elucidate whether specific deficits, such as naming or word retrieval problems may be influencing these outcomes (e.g. <sup>36</sup>).

The current data show that effects of cognitive improvement due to cortical growth and restrictions in verbal cognitive development with anterior temporal resections can co-occur within the same individual. As shown in Fig 3, one individual with anterior temporal resection showed increase of 22 IQ points over time. This individual experienced a decline in verbal IQ as associated with anterior temporal resection (VCI decrease from 77 to 70), and

simultaneously an increase in performance IQ measures (increase in POI/PRI from 63 to 104) and significant cortical growth. Similar effects were seen in two other individuals with anterior temporal lobe resections (VCI -9 and POI/PRI +19; VCI -9 and PRI/POI +8). This indicates that changes seen are not simply attributable to a global cognitive improvement or decline.

Replicating previous results, longer follow-up was associated with greater post-surgical improvement, highlighting the importance of carrying out routine long-term follow-up assessments to identify reliable changes.<sup>8,9</sup> No association was seen between IQ change and age at surgery. However, this finding does not clarify the potential cost of delaying intervention for cognitive outcomes.<sup>37</sup> The average duration between epilepsy onset and surgery in our study was 7.5 years. Shorter duration of epilepsy has been associated with better pre-surgical cognitive functioning<sup>38</sup> and better long-term seizure control.<sup>39</sup> However, since age at onset, duration of epilepsy and age at surgery are intercorrelated, larger cohorts are required to clarify interactions between these factors to identify critical periods for intervention and optimized outcomes.

In contrast to previous studies, IQ change in this cohort was not significantly influenced by post-surgical cessation of seizures<sup>3,8</sup> or AED treatment.<sup>4,9,15</sup> The more limited post-surgical use of Topiramate in the current sample, may account for differences in relation to other cohorts (e.g. <sup>9</sup>). Negative impacts of Topiramate on cognition have been identified in previous randomized studies.<sup>40,41</sup> Furthermore, the effects of seizure and AED reduction/cessation may be graded rather than categorical: in the current study patients who became seizure and AED free (n=20) showed an average 9 point increase in FSIQ, compared to +4 in seizure-free patients who continued AED treatment (n=7), +2 for those with reduced seizure frequency (n=6), and a 6 point decrease in those with unchanged seizure frequency (n=5).

Although practice effects have been noted for IQ assessments, in particular for performance IQ measures (PRI/POI)<sup>42</sup>, changes in FSIQ or component scaled scores were not correlated with the number of IQ assessments conducted with each individual. Practice effects may have been limited in the current study due to the typically long duration between assessments (median 3.4 years), which is likely to have reduced carry over or learning effects.

Our participants were selected on the basis of available preoperative cognitive data and availability for neuroimaging and cognitive assessments. We noted a modest but significant difference of IQ at baseline between individuals who were recruited into the study and those that were not. It is not clear whether these differences were due to greater difficulty for some participants to attend follow-up investigations (perhaps due to greater inflexibility of work, educational or support arrangements, or more difficulty with travel and participating in cognitive and MRI assessments). Efforts are now required to promote inclusivity, for example through mobile or home-based assessment options, and more flexible or proximal options for MRI imaging, to promote broader participation, and further improve accuracy of outcome data.

Whilst a waiting list randomization study of paediatric epilepsy surgery with a 12 month follow-up has recently been published,<sup>43</sup> it is not feasible to examine longer-term outcomes in this manner.<sup>8,13</sup> Children matched for basic illness characteristics provide a suitable comparison group for estimating developmental trajectory in epilepsy without surgical intervention.<sup>15</sup> Although there was in part overlapping pathological diagnoses between surgical and non-surgical participants, participants in the non-surgical group also had pathological diagnoses that were not represented in our surgical sample. This control group allows us to control for potential sources of bias in our results, including the impact of epilepsy-related developmental variables, and the effects of regression to the mean in repeated assessments. However the non-surgical group also differed from the surgical sample on a number of characteristics, including lower baseline seizure severity and younger age at follow-up. Although this study provides insights into post-surgical IQ development, replication is required, and multicenter studies are needed to clarify outcomes where a variety of interacting or additive factors are operating.

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**Author contributions**

Contributions from authors are as follows: study conception and design (JHC, TB, FV-K), data collection and analysis (all authors), writing manuscript and critical revision (all authors).

**Ethical publication statement:**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Data are reported following STROBE case-control guidelines, identified as the most appropriate reporting guideline through the Equator Wizard (<https://www.penelope.ai/equator-wizard>). Selected data can be obtained from the authors on request.

**Disclosure of conflicts of interest**

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