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Do behavior and emotions improve after paediatric epilepsy surgery? A systematic review

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Short title: Behavioral outcomes after paediatric epilepsy surgery

Summary

Objective: The objective was to systematically review studies which have focussed on the behavioral and emotional functioning before (baseline) and after (follow-up) paediatric epilepsy surgery. **Methods:** The systematic review was carried out according to PRISMA guidelines. Pubmed and Embase were searched from inception. Findings are described with respect to 1.) Changes in behavior and emotions between baseline and follow-up 2.) Factors associated with changes in behavior and emotions 3.) The impact of study quality on findings. **Results:** Fifteen studies met inclusion criteria. The majority of studies employed parent report screening checklists. In these studies scores were reported to have significantly improved at follow-up on at least one domain in seven studies and not changed significantly in two studies. In no studies was a deterioration in behavior noted. In studies which used DSM clinical diagnoses, no significant change was noted in the numbers of children diagnosed at baseline and at follow-up. In total 21 children lost diagnoses whilst 16 children developed new diagnoses. A better seizure outcome was associated with improvements in behavioral-emotional functioning at follow-up in three of the four studies where it was considered. In terms of study quality none of the studies were rated as strong (i.e. had no weak ratings on a quality assessment tool). **Significance:** There is some evidence of improvement in emotional and behavioral functioning after epilepsy surgery. However, this is confined to scores on parent reported screening measures of emotional and behavioral symptoms and not clinical diagnoses. Future research should focus on including responses from multiple respondents (child, parent, teacher) when using screening instruments, but also diagnostic interviews. There is a need for long-term follow-up (beyond 2 years) with sufficiently large samples sizes including data from non-surgery controls to understand factors associated with changes in functioning post-surgery.

Introduction

Children are typically referred for epilepsy surgery if their seizures have demonstrated a failure to respond to antiepileptic drugs (AEDs), usually defined as the failure of adequate trials of two tolerated and appropriately chosen AED schedules, either as monotherapy or in combination. Approximately one quarter of children with epilepsy have seizures which do not respond to either of the first two prescribed AEDs², and 1 in 4 of these children are considered to have potentially surgically remediable epilepsy syndromes³.

As well as recurrent unpredictable epileptic seizures, children with epilepsy are at increased risk for a range of behavioral and emotional difficulties including diagnoses of autism spectrum disorder (ASD), disruptive behavior disorders, attention deficit hyperactivity disorder (ADHD), depression and anxiety^{4,5}. These difficulties often have a greater impact than the seizures themselves on Health Related Quality of Life (HRQOL)^{6,7} but are often not identified or treated⁴. In children undergoing epilepsy surgery high rates of psychiatric comorbidity have been noted for both temporal lobe and extratemporal lobe cases^{8,9}.

Epilepsy surgery in children is successful with respect to seizure reduction and/or freedom¹⁰ and improved quality of life¹¹ provided there is appropriate selection of candidates. There is also evidence that at least some children have gains in cognition¹² but the situation is less clear with regard to emotional and behavioral functioning and psychiatric diagnoses. Having greater knowledge of the impact of epilepsy surgery on behavior and emotions will add to an understanding of the broad psychosocial impact of epilepsy surgery and aid pre-surgery counselling.

The purpose of the current review was to systematically evaluate studies which have focused on measures of psychopathology (behavior and emotions) before and after paediatric epilepsy surgery. The first objective was to describe changes in functioning on assessment measures of behavior and emotions between pre-surgery assessment and follow-up after surgery. An additional aim was to consider factors associated with changes in behavioral and emotional functioning. A final aim was to consider the impact of study quality on findings.

Methods

The review was carried out adhering to PRISMA guidelines <http://prisma-statement.org/>. A literature search was conducted on 5th June 2018. The electronic databases PubMed and EMBASE were searched from inception to the present using different combinations of the following keywords: epilepsy, surgery, children, pediatric, behavior/behavior, emotions, psychopathology, anxiety and depression from inception to June 5th 2018. The combinations searched are in supplementary table 1.

Inclusion criteria were: participants had undergone epilepsy surgery, sample size ≥ 10 , published in English, majority of participants were children (0-17 years) at time of surgery, the study included a standardised validated measure of behavior/emotions or behavioral/emotional diagnoses were made with respect to DSM/ICD criteria. Studies were included where there was data on behavior/emotions before surgery (baseline) and after surgery (follow-up).

Studies which only had measures of cognition, adaptive behavior, quality of life (even if the instrument included aspects of behavior or emotions) and executive functioning were excluded.

A data extraction form was developed (see supplement 2) which focussed on extracting the main study characteristics and results. Data was independently extracted by two reviewers (SW & NS) with any differences being resolved by consensus or discussion with a third reviewer (CR). The review was registered at <https://www.crd.york.ac.uk/PROSPERO/>.

Results are reported with respect to changes in total scores on standardised measures within the group who underwent surgery and with respect to non-surgery controls. Non-surgery controls were children who had seizures which did not respond to AEDs but who did not undergo epilepsy surgery. Additionally results are reported where relevant with respect to change in clinical classification (i.e. met criteria for a psychiatric/behavioral diagnosis).

A ‘significant’ change in functioning is defined as a change is significant at the $p < 0.05$ level using an appropriate repeated measure statistical analysis.

Factors associated with change are only reported where a statistical analysis was undertaken. Results are reported as ‘significant’ where p-values are less than $p < 0.05$.

Study Quality

All studies were assessed for quality using the Effective Public Health Practice Project (EPHPP) tool quality rating tool (http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf accessed May 3rd 2018). This measure includes six questions focusing on selection bias, study design, confounders, blinding, data collection methods, and withdrawals and drop-out. Ratings on the six questions are used to derive a global rating which can be ‘Strong’ (no weak ratings), ‘Moderate’ (one weak rating) and ‘Weak’ (two or more weak ratings) and these are reported

on in the current study. In some cases the questions needed to be adapted/interpreted and these adaptations are noted in Supplement 3. Study quality for all studies were rated independently by CJ and CR. Disagreements were resolved by consensus.

Results

The results of the systematic search are in Figure 1. The number of unique papers after duplicates were removed was 104. Abstracts of these papers were reviewed to see if they met inclusion criteria; after screening 15 studies could be included.

Table 1 shows the clinical characteristics of the study participants in all studies. More detailed information is available on all studies in Supplement 4.

The studies took place in Canada (4), UK (3), Italy (3), Sweden (1) India (1), USA (1) and Germany (2). All studies focused on a mixed pathology group. In terms of surgery type, 12 of the 15 studies focused on a mixed group whereas one focused solely on temporal lobe surgery⁸ one focused solely on patients who had undergone hemispherectomy²¹ and one on parietal lobe surgery. Sample size for those who underwent surgery ranged from 10 to 147. Six of the 15 studies contained controls with difficult to treat epilepsy who did not undergo surgery^{13,14,15,16,22,25}.

Table 2 shows the main findings with respect to measures of behavior at baseline and at follow-up after surgery.

The Child Behavior Checklist (CBCL)²⁶ was the mostly widely used measure of behavioral and emotional functioning, being used in 10 of the 15 studies. In only one study was a self-report measure used where the children undergoing surgery responded and in this study the self-report measures focused on anxiety and depression¹⁷. Mean follow up time from baseline to follow-up assessment ranged from 3 months to 6.7 years.

Parental screening measures

Significant improvements in at least one behavioral domain on parental screening measures were noted in seven^{13,15,16,19,22,25} of nine studies where it was possible to evaluate significant change and in no study was there a significant worsening on any subscales. The total score on the CBCL showed improvement in three studies^{13,23,25} and the total score improved on the Strengths and Difficulties Questionnaire (SDQ)²⁷ in the one study where it was used¹⁹. Regarding the numbers who scored in the at-risk/not at risk zone on measures of behavioral and emotional functioning, Lendt et al.²⁵ reported that in the surgery group the classification had improved significantly on CBCL total behavior whilst in the control group more children were in the abnormal group than at baseline.

DSM-IV diagnoses

In the studies which employed DSM-IV diagnoses no significant change was noted in the proportion of children diagnosed with psychiatric disorder between baseline and follow-up although it was noted that a small number of children lost diagnoses whilst in others diagnoses were gained^{8,9,20,21}. McLellan et al. reported that 9/57 (16%) children who had a psychiatric diagnosis at baseline did not have a diagnosis at follow-up whilst 7/57 (12%) who had been free of psychopathology had developed a psychiatric condition at follow-up. Colonelli et al.⁸ reported that 8/71 (11%) children who had met criteria for a psychiatric diagnosis no longer

had a diagnosis at follow-up whilst in 6/71 (9%) without a diagnosis at baseline had a diagnosis at follow-up. Danielsson et al.²⁰ reported that one child (4%) with a psychiatric diagnosis at baseline did not have a diagnosis at follow-up whilst 3/24 (12%) without a diagnosis had developed a psychiatric condition at follow-up. In eleven patients who underwent hemispherectomy with baseline and follow-up data Lettori et al.²¹ reported that none who without a diagnosis at baseline acquired a diagnosis at follow-up whilst three with at least one diagnosis at baseline acquired were diagnosis free at follow-up.

Comparisons with non-surgery controls

In comparisons to controls Dwivedi et al.¹³ reported that the surgery group had significantly greater change in scores on CBCL total score (12.3 point reduction) than the non-surgery group (0.8 point increase). This finding is from the only Randomised Control Trial in paediatric epilepsy surgery was supported by two other cohort studies for parental ratings on the CBCL. Elliott et al.²² reported a group by time interaction showing post-surgical improvements of parental ratings on the social and social problems subscales whereas in the non-surgery group a decline over time was noted. Lendt et al.²⁵ reported that mean CBCL scores for the surgery group had decreased at follow-up. However, two reports both from the same centre did not find an effect of surgical status on changes in functioning.^{15,16}

Factors associated with change in behavior or emotions

The evaluation of clinical factors associated with change in behavior or emotions between baseline and follow-up is shown in table 3.

In relation to post-surgical seizure outcome three out of four studies found that better seizure control was associated with improvements in at least one aspect of behavior or emotions^{15,24,22}

No other factors were found to be consistently associated with changes in psychopathology between baseline and follow-up. A summary of all findings is in Supplement 5.

Study Quality

The consensus ratings of study quality are in supplement 3.

Five of the 15 studies were given a moderate rating. The rest were given a weak rating. None of the studies were given a strong rating.

Only one study was given a good rating regarding selection bias¹³ as the study participants appeared to drawn from all possible patients had who undergone surgery in a specified geographical areas. This RCT study¹³ this was also the only study given a strong rating with respect to study design.

‘Blinding’ refers to whether the assessors of child psychopathology are aware which groups were in control or surgery groups and in none of the studies was it apparent that assessors of the child’s behavior were blinded to the surgery status.

The ‘confounders total’ is based on whether control and surgery groups were well matched and in most studies where controls were included they were judged to be well matched on important clinical factors. Studies without controls were automatically rated as ‘weak’ with respect to this question. None of the studies which employed DSM-IV diagnoses had a control group.

All but three studies used standardised rating scales such as CBCL or SDQ and were rated as strong as these measures are reliable and valid^{28,29}. Two studies used case notes review and were rated a strong because this method is also reliable and valid²⁹. Regarding the issue of participant withdrawals, studies were categorised as strong if there appeared to be no drop outs. All but four studies had a 'strong' rating.

Discussion

This review suggests that at a group level children who undergo epilepsy surgery may have improved emotional and behavioral functioning on parent-reported measures at follow-up. In studies where the presence or absence of psychiatric disorder was measured, only a small number of children lose a diagnosis of a psychiatric disorder after surgery. Additionally a small number of children develop a new psychiatric condition post-surgery. Seizure freedom was associated with an improved behavioral or emotional outcome in three of four studies where it was evaluated. With respect to study quality none of the included studies were rated as 'strong' highlighting the need for more robust study designs.

A significant improvement in parent reported psychopathology in the majority of studies, including in the only randomised control study, suggests that the majority of parents perceived improved behavior in their children post-surgery. However, the improvement in functioning noted on behavioral checklists was not mirrored in studies which focused on categorical clinical diagnoses. This suggests that dimensional measurement of symptoms in this population reveals improvement, whereas studies employing categorical change does not capture differences as sensitively. It could be that although statistically significant, the symptom changes are not great enough to result in loss of a diagnosis. It may also be that that symptom

measures do not capture aspects such as functional impairment, or onset and duration of symptoms which are needed to make a psychiatric diagnosis. Additionally, relying exclusively on parent report may not be optimal given potential bias due to prior expectations and seizure outcome.

In studies where clinical diagnoses were used some children lost diagnoses while others gained new diagnoses highlighting that there may be significant individual variation with respect to outcome. Reasons why a small number of children develop a new psychiatric diagnosis post-surgery could include that the child's behavioral difficulties become more apparent after previously being 'masked' by frequent seizures or AED usage. Another possibility is that the child has difficulties adjusting to life after epilepsy surgery. Epilepsy surgery patients may experience difficulty transitioning from chronic disability to sudden wellness and adjusting to this 'burden of normality'³¹ or alternatively dealing with disappointment if seizure freedom/reduction is not achieved. An additional possibility is that it could simply be that new disorders are emerging by chance as children age. Childhood psychiatric disorders are common, and tend to increase with age. A UK epidemiological study showed that 5.5% of 2 to 4 year old children experienced a mental disorder, compared to 16.9% of 17 to 19 year olds (<https://www.gov.uk/government/statistics/mental-health-of-children-and-young-people-in-england-2017-pas> accessed December 4th 2018).

Studies which have included controls with treatment resistant epilepsy who do not undergo epilepsy surgery have shown mixed results - with three studies showing significantly better outcomes in the surgical compared to control group on at least some domains of behavior^{13,22,25}, whilst two other studies showed no significant differences^{16,15}. None of the studies have shown

that controls have had better outcomes than the children who underwent surgery. Differences in findings likely reflect sample composition (e.g. measures used), and follow-up duration.

A good seizure outcome appears to be associated with better behavioral outcome on parent reported measures but this was considered in only four studies. Long-term health related quality of life in children who have undergone epilepsy surgery has been shown to be associated with seizure freedom^{12,32,33} but also with presence of depression and anxiety symptoms³⁴. AEDs were not associated with changes in psychopathology. However, the studies have not considered change in AED use from before to after surgery as a predictor. Given that reduced AED use and complete AED withdrawal are associated with improved post-operative IQ^{12,35} it is important to consider any change in AEDs in future studies. Change in IQ between baseline and follow-up was not associated with behavioral change but this was only considered in one study. No clear patterns emerged regarding other factors which were considered as possible predictors of change in psychopathology between baseline and follow-up.

Implications for clinical practice and future research

There is scope for optimism when counselling families regarding emotional and behavioral change post epilepsy surgery – symptoms rarely worsen and the majority of studies show some symptomatic improvement. However, the lack of significant changes in studies which have employed DSM-IV diagnoses means that optimism should be tempered with the need to counsel parents about the uncertainty of outcome. The high level of behavioral and emotional difficulties in children with epilepsy^{4,15} and potential for effective treatment, highlights the need to assess for such difficulties in all children being considered for surgery. Detection of common mental health problems in children with epilepsy, such as challenging behavior,

attention deficit hyperactivity disorder, depression and anxiety, warrants referral for standard evidence-based treatments. The high-rates found in epilepsy surgery patients indicates that this is a particularly vulnerable group with rates of 52% to 83% in the studies reported here^{8,9,20}.

This systematic review highlights the diverse range of methods used to assess behavior and emotions in paediatric epilepsy surgery. Studies have not employed diagnostic interviews based on international classification systems (e.g. DSM) and these should be employed in tandem with behavioral checklists. Few studies have employed disorder specific checklists and thus there is a need to use screening instruments for ADHD, oppositional defiant disorder, autism, depression and anxiety the most common comorbid behavioral and emotional difficulties in the paediatric epilepsy population^{4,5} to better understand if there are differences in changes according to the assessed domain. There is also a need to use self-report and teacher-report given that these respondents can often differ significantly from parental reports of psychopathology in children with epilepsy^{36,37}. It is additionally important that appropriate validated instruments are used with respect to child age and intellectual functioning. Future studies will also be more robust if assessors of functioning are blind to a child's surgical status and/or pre-operative behavioral functioning if possible.

There was no discernible pattern regarding change in behavior and emotions between studies with short (12 months or less) and longer (greater than 12 months) follow-up periods with improvements evident in both follow-up periods. The need to conduct follow up assessments over an extended period of time (more than 2 years) is crucial given that any changes in behavior may only become apparent with time as has been shown for some children with respect to IQ after surgery¹². Epilepsy surgery techniques continue to develop and with newer techniques and technologies and this could impact on changes in behaviour. There on parental

ratings of behaviour improvements were noted in the earliest conducted studies and studies conducted more recently but this not preclude the possibility that new techniques could influence outcome. Published studies have not considered the potential impact of supports received for emotional and behavioural difficulties between surgery and follow-up. This needs to be considered as interventions for these difficulties may significantly affect functioning.

Family functioning has been shown to be important in psychopathology in children with epilepsy³⁸ and should also be considered in future studies especially since significant improvements in parental wellbeing after surgery have been shown³⁹. The high rates of depression and anxiety parents of children with epilepsy report^{40,41} could also influence reporting of child functioning and thus considering parental functioning will be useful with respect to understanding potential discrepancies between parent and child report. Regarding neuropathology, types of surgery and laterality, there is a need for larger sample sizes with segregated design to better understand if specific underlying pathologies are associated with better outcomes. A consistent pattern of findings has not been found between duration of epilepsy or age of onset but these were only considered in two studies and future studies need to consider a wide variety of epilepsy related factors.

Conclusion

There is some evidence of improvement in behavior and emotions after surgery but this is confined to parent reported symptoms on behavioral checklists. The use of a wide range of assessment instruments and methods of reporting and analysis makes synthesis, comparison and interpretation across studies difficult. There is a clear need for prospective, adequately powered studies employing both checklists and diagnostic interviews and asking multiple informants about the presence of child psychopathology. Such studies need to consider a wide

range of possible contributors to change in functioning over longer periods of time to better understand reasons why some children appear to improve but others do not.

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Disclosure of Conflict of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Key Points

- In studies employing parent report checklists, behavior and emotions improved at follow up in the majority of studies
- In no studies was a deterioration in behavior or emotions noted at follow-up
- In studies which used DSM clinical diagnoses, no significant change was noted between baseline and follow-up

- Better seizure outcome was associated with improvements in behavioral emotional functioning

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Figure 1: Selection of studies -Pubmed and Embase search

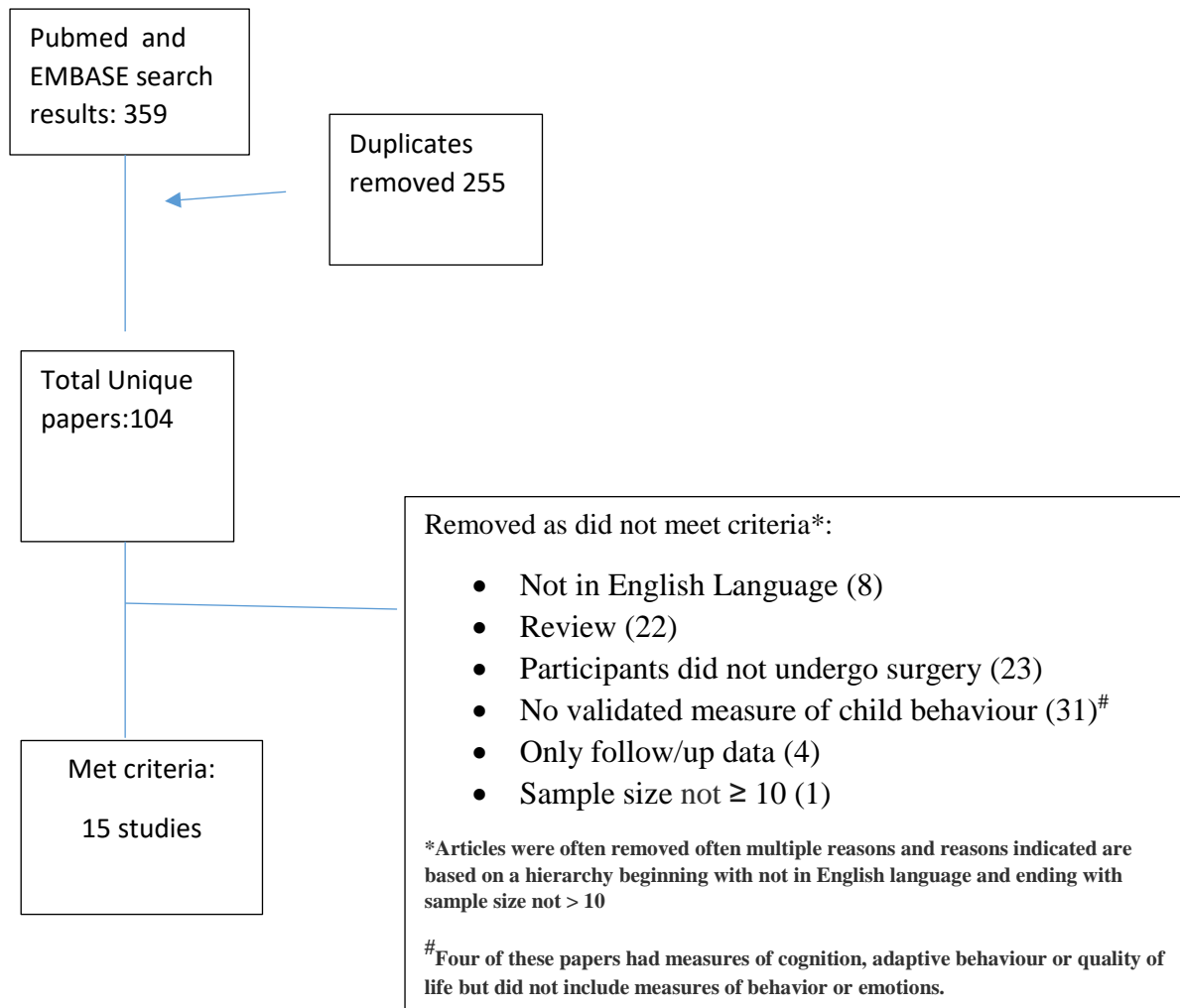


Table 1 Characteristics of children in studies which have focussed on behaviour and emotions at baseline and follow-up after paediatric epilepsy surgery

| Authors | Year published | Country and Centre | Sample Size (m/f) | Age at T1 assessment/Surgery Mean/Range | Age at seizure onset Mean/Range | Seizure frequency at baseline | Seizure frequency/outcome at follow-up | Type of surgery | AEDs baseline/follow-up |
|------------------------------|----------------|--------------------|--|--|---|---|--|--|--|
| Dwivedi et al. ¹³ | 2017 | India, New Delhi | Surgery 57 (34/23) Control 59 (40/19) | Surgery 9*(0.8-17) Control* 10 (2-17) | Surgery 1.5* (0.1-9) Control 3* (0.1-10) | <u>Surgery</u> ≥1 Per day 48 ≥1 Per week 5 ≥1 Per mo 4 ≥1 Per 3 mo 0 <u>Control</u> ≥1 Per day 40 ≥1 Per week 10 ≥1 Per mo 6 ≥1 Per 3 mo 0 3 | <u>Surgery</u> Complete freedom (44) <u>Control</u> Complete freedom (4) | Temp. 14 Extrat. 12 Hemis. 15 CorpCal 10 HyopH 6 | <u>Baseline</u> Surgery 3* Control 3* <u>Follow-up</u> NR |
| Sibilia et al. ¹⁴ | 2017 | Florence Italy | 31 Surgery (20/11) 14 Control (5/9) | Surgery 8.73 Control 10.26 | Surgery 4.41 Control 4.89 | <u>Surgery</u> Daily (16) Daily (1) Weekly (7) Monthly (7) <u>Control</u> Daily (5) Daily (2) Weekly (2) Monthly (5) | <u>Surgery</u> Engel Class I (25) Engel Class II (3) Engel Class III (3) <u>Control</u> Engel Class III (5) Engel Class III 9) | Unilobar 17 Multilobar 7 Unilobar – Extrat 7 | <u>Baseline</u> <u>Surgery</u> Polytherapy 31 <u>Control</u> Polytherapy 10 Monotherapy 4 <u>Follow-up</u> <u>Surgery</u> Monotherapy 15 Polytherapy 6 2 no Aeds <u>Control</u> All on Polytherapy |
| Puka & Smith ¹⁵ | 2016 | Canada, Toronto | Surgery 71 (30/41) Control 37 (11/28) | Surgery 12.98 (4.25-18.83) | Surgery 5.77 (NR) Control 4.69 (NR) | NR | <u>Seizure-free</u> Surgery 54.9% Control 37.8% | Lesionectomy 14 Corticectomy 17 Lobectomy 40 | <u>At follow up – Not taking AEDs</u> Surgery 28 Control 5 |

| | | | | | | | | | |
|-------------------------------|------|-------------------|---|---|---|--|---|---|--|
| Law et al. ¹⁶ | 2015 | Canada Toronto | Surgery 147 (72/75) Control 40 (20/20) | Surgery 11.56 (2.98- 17.88) Control 11.94 (2.94-18.01) | Surgery 5.80 (4.46) Control 5.14 (3.90) | NR | <u>Seizure Outcome</u> <u>Surgery</u> Seizure free (95) Continuing seizures (52) <u>Control</u> Seizure free (8) Continuing seizures (32) | Temp. 68 Front. 20 Occip. 4 Pareit. 4 Multi. 51 | <u>Baseline</u> Surgery 1.79 (0-4) Control 1.83 (0-3) <u>Follow-up</u> Surgery 1.73 (0-4) Control 1.82 (1-3) |
| Andresen et al. ¹⁷ | 2014 | USA, Cleveland | 100 (51,49) | 10.96 (6-16) | 5.81 (NR) | NR | Engel class I (84) Engel class II (5) Engel Class III (4) Engel Class IV (7) | Temp. 64 Front. 36 | <u>Baseline</u> 2.10 <u>Follow-up</u> 1.68 |
| Colonelli et al. ⁹ | 2012 | UK, London | 71 (38/33) | 9 (0.4-18 years) | 9 (NR) | Daily 49 Weekly 19 Monthly 3 | Seizure free since surgery (35) | Front 52 Pareit. 12 Occip. 7 | <u>Baseline</u> mean 2 (range 1-3) <u>Follow-up</u> Median 2 (range 1 to 3) |
| Chieffo et al. ¹⁸ | 2011 | Italy, Rome | FLE 12 (7/5) TLE 12 (8/4) | FLE 7.5 (1.17 - 17) TLE 8.2 (0.75 - 17) | FLE 5.6 (0.66- 12.2) TLE 5.8 (0.25 -14.6) | <u>FLE</u> Daily 3 Weekly 4 Monthly 3 Yearly 2 <u>TLE</u> Daily 2 Weekly 7 Monthly 2 Yearly 1 | <u>FLE</u> Engel Class I (11) Engel Class II (1) <u>TLE</u> Engel Class I (10) Engel Class II (2) | Frontal. 12 Temp.12 | <u>FLE</u> <u>Baseline</u> Greater than 2 (5) <u>Follow-up</u> Greater than 2 (0) <u>TLE</u> <u>Baseline</u> Greater than 2 (5) <u>Follow-up</u> Greater than 2 (0) |
| Hannan et al. ¹⁹ | 2009 | UK, London | Surgery 13 (4/9) | 10.8 (5-17) | 2.07 (<1 month - 9years) | NR | Class IA (8) Class IV (3) Class II (2) | Hemis. 4 Temp. 6 Extra. 2 MST 1 | NR |

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|---------------------------------|------|--------------------|--|---|--|--|--|---|--|
| Danielsson et al. ²⁰ | 2009 | Sweden, Gothenburg | Surgery 24 (15,9) | 12.64 (4.2-19.4) | NA | Mean monthly 114 Range 5-450 | Class I (7) Class II (7) Class III (5) Class IV (5) | Temp. 9 Front. 8 Pariet. 2 Occip. 2 Hyopt. H 3 | NR |
| Lettori et al. ²¹ | 2008 | Italy, Rome | Surgery 19 (11,8) | 2 (2.25-5.42) | 0.25 (0.01 – 2.66) | All had daily seizures | Class I (14) Class II (2) Class III (3) | Hemis. | Baseline 4.26 (2-7) Follow-up 1.26 (0-3) |
| Elliott et al. ²² | 2008 | Toronto, Canada | Surgery 20 (8/12) Non-Surgical 12 (4/8) | Surgery 13.7 (8.6-18.3) Control 13.4 (7.35-18) | <u>Surgery</u> 6.9 0-12.5 years <u>Control</u> 6.9 0-13 years | NR | <u>Surgery</u> Time 2 11 seizure free Time 3 10 seizure free | Temp 11 Extra. 6 Multi. 3 | <u>Follow-up (Time 3)</u> Surgery 1.9 Control 2.2. |
| Gleissner et al. ²³ | 2008 | Bonn, Germany | Surgery 15 [#] (2,13) | Surgery 11 (6-15) | Surgery 6.1 (1-12) | NR | 13 seizure free at follow-up | Parietal | Pre 2 (1-3) Post 1.27 (1-2) |
| McLellan et al. ⁸ | 2005 | UK, London | Surgery 60 (35,25) | 10.58 (7-17.92) | 3.5 | Mean 98 seizures a month | Class I (34) Class II (3) Class III (9) Class IV (11) Lost to follow up (3) | Temp. | NR |
| Sinclair et al. ²⁴ | 2004 | Canada, Alberta | Surgery 35 (14/21) | 6-16 | NR | NR | Class I (24) Class II (1) Class III (6) Class IV (4) | Front. 12 Hemis. 10 Pariet. 8 Occip. 4 Hypoth H 1 | NR |
| Lendt et al. ²⁵ | 2000 | Germany, Bonn | Surgery 28 (14/14) Control 28 (18/10) | Surgery 11.5 (5-16) Control 10.3 (4-16) | Surgery 5.6 (0-15) Control 5.4 (0-15) | Median Surgery 17.5 Surgery 30.0 | <u>Surgery</u> Seizure free (21) 50% reduction (5) Unchanged (2) <u>Control</u> Seizure free (4) 50% reduction (6) Unchanged (18) | Temp. 13 Pariet.-occip. 7, Front. 4, Hemis 2, Corpcal 2 | Baseline <u>Surgery</u> None 1 Monotherapy 3 Polytherapy ₂₄ <u>Control</u> None 1 Monotherapy 8 Polytherapy ₁₉ |

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*Median, NR= Not reported, Temp.=Temporal, Extra.=Extratemporal, Hemis. =Hemispherectomy, Corpcal.= Corpuscallosotomy, Hypo H= Hyothalamic Haemerthoma, Front.= frontal, Pareit.=Parietal, MCD= Malformation of cortical development, MTS= Medial Temporal sclerosis, Occip.= Occipital, #Behavioural data was only available for 10 patients

Table 3: Factors significantly associated with change in behaviour or emotions in children who have undergone surgery

| Authors | Year | Seizure Outcome status | Baseline Score | Age at surgery | sex | Age at onset | Duration of epilepsy | Site of surgery | Side of surgery | IQ | Time between surgery and follow up | AEDs |
|-------------------|------|------------------------|----------------|----------------|----------|--------------|----------------------|-----------------|-----------------|------------|------------------------------------|----------|
| Dwivedi et al. | 2017 | - | - | - | - | - | - | - | - | - | - | - |
| Sibilia et al. | 2017 | - | - | - | - | - | - | - | - | - | - | - |
| Puka & Smith | 2016 | sig. | sig. | sig. | -- | -- | -- | not sig. | not sig. | not sig.* | -- | not sig. |
| Law et al. | 2015 | not sig. | -- | -- | -- | sig. | -- | sig. | sig. | not sig.** | not sig. | -- |
| Andresen et al. | 2014 | -- | -- | -- | -- | -- | -- | sig. | -- | -- | -- | -- |
| Colonelli et al | 2012 | - | - | - | - | - | - | - | - | - | - | - |
| Chieffo et al | 2011 | - | - | - | - | - | - | - | - | - | - | - |
| Hannan et al. | 2009 | - | - | - | - | - | - | - | - | - | - | - |
| Danielsson et al. | 2009 | - | - | - | - | - | - | - | - | - | - | - |
| Lettori et al. | 2008 | - | - | - | - | - | - | - | - | - | - | - |
| Elliott et al | 2008 | Sig. | -- | -- | -- | not .sig | not. sig | -- | -- | -- | -- | not sig. |
| Gleissner et al. | 2008 | - | - | - | - | - | - | - | - | - | - | - |
| McLellan et al. | 2005 | - | - | - | - | - | - | - | - | - | - | - |
| Sinclair et al | 2004 | - | - | - | - | - | - | - | - | - | - | - |
| Lendt et al. | 2000 | sig | not sig. | not sig. | not sig. | not. sig. | not sig. | not sig. | not sig. | -- | -- | -- |

- =Not applicable as no statistical analysis or unclear analysis carried out on factors associated with change in behavioural or emotional symptoms, -- = Not included in the analysis *Change in IQ, **baseline IQ

Table 2: Measures of behaviour and emotions before and after surgery

| Authors | Year (s) of surgery | Follow-up time | Instrument | Cognitive level at baseline (FSIQ unless otherwise stated) | Main Findings |
|-----------------|---------------------|--|------------------|---|--|
| Dwivedi et al. | 2010-2015 | 12 months | CBCL | 63.9 Surgery (n=30) 62.8 Control (n=33) | <ul style="list-style-type: none"> • CBCL T-score[#] reduced significantly (i.e. better functioning) from 69.5 to 57.2 in surgery group • CBCL T-score increased from 67.8 to 68.6 in controls. |
| Sibilia et al. | 2007-2011 | 12 months | CBCL | Surgery 74.35 Controls 82.07 | <ul style="list-style-type: none"> • At follow-up a non-significant decrease in CBCL Total, internalising and externalising scales. |
| Puka & Smith | 2002-2009 | 6.69 years (4-11 years) | CBCL/ABCL | Surgery 80.70* Controls 81.28* | <ul style="list-style-type: none"> • Among all groups (i.e. surgery seizure free, surgery not seizure free, non-surgery seizure free and non-surgery not seizure free) scores on externalising behaviour, thought problems, attention problems improved significantly from baseline to follow up. • No significant changes in baseline to follow-up categorisations for surgical or control groups |
| Law et al. | NR | 12 months | CBCL | Surgery VIQ 86.03 PIQ 88.10 Controls VIQ89.30 PIQ 83.95 | <ul style="list-style-type: none"> • Significant improvements for externalising behaviour and total competence in both surgery and non-surgery groups. • No change in CBCL classifications for surgery group but in controls significantly more were in abnormal range on internalizing scale at follow-up |
| Andresen et al. | 1992-2012 | Mean 8.5 months | CBCL, CDI, RCMAS | 84.12 | <ul style="list-style-type: none"> • Left-Sided - Children with FLE had higher levels of difficulties on all three scales but improved on all three whereas TLE remained stable. • Right-Sided - Patients in both groups improved. FLE in general had higher scores both before and after but also showed greatest improvement. |
| Colonelli et al | 1997- 2008 | 12 months | DSM-IV criteria | Pre 42% ID (IQ<70) Post 37% ID (IQ<70) | <ul style="list-style-type: none"> • 52% had a mental health diagnosis at some point in time. A similar proportion had a diagnosis pre (44%) and post-surgery (45%) • Postoperatively eight children who previously had a diagnosis did not have a diagnosis at follow-up whilst, six developed a diagnosis postoperatively. |
| Chieffo et al | NR | FLE 2.10 (1-6.5 years) TLE 3.4 (1- 6.4 years) | CBCL | FLE-abnormal (>1SD)17% pre and post-surgery TLE -abnormal (>1SD – 25% pre and 33% post-surgery | <ul style="list-style-type: none"> • FLE - 50% had a behaviour disorder before and 17% after • TLE - 50% had a behaviour disorder before and 17% after |

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|-------------------|-----------|---|--|--|---|
| Hannan et al. | 1997-1998 | Four time points ranging from. Pre-surgery to 8 years | SDQ | 2 Normal 3 Mild ID (FSIQ 50-70) 4 Moderate ID (FSIQ 35-49) 4 Severe ID (FSIQ <35) | <ul style="list-style-type: none"> Scores significantly lower between Time 1 and Time 2, Time 3 and Time 4 |
| Danielsson et al. | 2002-2006 | 2 years | Clinical assessment based on DSM-IV criteria | Baseline IQ>70 14 IQ50-69 1 IQ35-49 6 IQ20-34 1 IQ<20 1 | <ul style="list-style-type: none"> 14 had a psychiatric disorder at baseline and 16 at follow up |
| Lettori et al. | 1980-2003 | 6.6 (2-11.17) | Behavioural disorder based on DSM-IV | Before – mean FSIQ 41.8 range 25-89 After mean FSIQ 39.79 Range 12-85 | <ul style="list-style-type: none"> Pre - 8/11 had a behavioural disorder Post – 12/19 had a behavioural disorder |
| Elliott et al | 1997-1999 | 2 years | CBCL | Surgery FSIQ 85.2 (52-137) Non Surgery FSIQ 81.6 Range 52-113 | <ul style="list-style-type: none"> Parents in both groups reported improvements over time on total score, externalising, delinquent and aggression subscales of CBCL On social and social subscale scale of CBCL surgery group reported improvement over time whereas those in control group reported a decline in functioning. |
| McLellan et al | 1992-1998 | 5.1 years (range 2-10 years) | Case notes review based on DSM-IV | Normal 32 Mild ID 5 Moderate ID 13 Severe ID 10 | <ul style="list-style-type: none"> Pre – 43/60 (72%) had at least one psychiatric diagnosis. Post - 41/57 (72%) 9 who had a diagnosis before did not have after and 7 had developed a de novo psychiatric diagnosis at follow-up |
| Gleissner et al. | 1986-2007 | 12 months | CBCL | 80.8 | <ul style="list-style-type: none"> Total CBCL score had improved at follow-up |
| Sinclair et al | 1988-1998 | 1-10 years | CBCL | FSIQ 91.9 but no data on 17 patients some of whom had ID | <ul style="list-style-type: none"> No measurable changes in psychosocial functioning detected |

| | | | | | |
|-------------|-----------|----------|------|--|---|
| Lendt et al | 1996-1999 | 3 months | CBCL | Surgery 50-115 (80.7) Non-Surgery 54-119 (84.2) | <ul style="list-style-type: none"> • Surgery group showed significant improvements on CBCL internalising problems, externalising problems, attention problems and thought problems subscales. No change in controls • Reduction from 50% to 32% in borderline/abnormal categorisation on CBCL in surgery group (significant improvement) at follow-up. Increase in borderline/abnormal categorisation from 46% to 57% on CBCL in non-surgery group at follow-up (significant deterioration) |
|-------------|-----------|----------|------|--|---|

CBCL=Child Behavior Checklist, ABCL =Adult Behavior Checklist, VIQ= Verbal IQ, PIQ= Performance IQ, FLE= Frontal Lobe Epilepsy, TLE=Temporal Lobe Epilepsy, CDI=Child Depression Inventory, RCMAS=Revised Children's Manifest anxiety scale, SDQ= Strengths and Difficulties Questionnaires, *At follow-up –baseline not available #CBCL T-Score of less than 60 is considered normal NR=Not reported, ID=Intellectual Disability