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I, Krista J Qualmann, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Examining the Pediatric Epilepsy Surgery Population: The Prognostic Value of Central Nervous System Comorbidities in Proband and their Families

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Examining the Pediatric Epilepsy Surgery Population: The Prognostic Value of Central Nervous System Comorbidities in Probands and their Families

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by

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ABSTRACT

Objective: To determine prevalence of central nervous system (CNS) comorbidities in pediatric patients undergoing epilepsy surgery and their families, and correlate these findings with long-term seizure outcome.

Methods: Parents of children, age 0-17, with epilepsy who received resective surgery at Cincinnati Children’s Hospital Medical Center (CCHMC) between January 1, 2007 – June 30, 2012 were invited to participate in the study. A three-generation pedigree of epilepsy and its CNS comorbidities was collected via an online or telephone questionnaire from 52 participants. Surgery outcome classification by the International League Against Epilepsy (ILAE) scale was abstracted from an existing CCHMC clinical database. Proportions of affected probands and relatives were calculated and compared to the general population rates of individual comorbidities and the probands’ seizure outcome classification at their most recent follow-up evaluation.

Results: Probands had significantly higher rates of ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression and motor disability than the general population. First degree relatives (FDRs) had significantly higher rates of ADHD, autism, depression, and motor disability, and total relatives had higher rates of depression, epilepsy/seizures, and motor disability. Diagnoses of cognitive disability and autism in probands and autism in FDRs were associated with poorer surgery outcomes.

Conclusions: Epilepsy probands and their families have significantly higher rates of CNS comorbidities than the general population. Poorer long-term seizure outcomes following resective surgery were associated with diagnoses of autism or cognitive disability in probands.
and autism in FDRs. Together these data support evidence for a common pathophysiological mechanism between epilepsy and its comorbidities.
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INTRODUCTION

Epilepsy is a chronic neurological condition characterized by recurrent spontaneous seizures that is present in 1% of the general population [1]. This common, heterogeneous disorder encompasses a spectrum of symptoms and outcomes, resulting from both known and unknown etiologies [2]. Antiepileptic drug (AED) therapy is effective in approximately two-thirds of epilepsy patients, leaving one-third without good seizure control [1]. Epilepsy is defined as intractable after the failure of two or more AEDs, at which time alternative treatment options such as resective surgery may be considered. The timeliness of identification of intractability and alternate treatment options is important, as continued seizures in childhood may interfere with healthy brain development [3].

Patients with epilepsy have higher rates of comorbid central nervous system (CNS) conditions compared to the general population, including attention deficit hyperactivity disorder (ADHD) [4-6], anxiety disorder [5-7], autism spectrum disorder [5, 6, 8, 9], bipolar disorder [5, 7, 10], cognitive disability [6, 8, 11], depression [5-7], migraine [5, 6, 12] and motor disability [8, 11]. An increased prevalence of these comorbidities in the epilepsy population is well-established in the current literature and support the argument for a shared pathophysiological mechanism [12, 13]. Family history of seizures has previously been associated with the presence of behavioral disorders [13] and migraines [14] in epilepsy probands. These studies suggest that family history information is also relevant to the presence of comorbidities in epilepsy probands and further supports the hypothesis that these comorbidities are heritable with epilepsy. However, there have not been studies documenting whether or not these comorbidities are also present at higher rates in probands’ family members.
Worse seizure outcomes following temporal lobectomy have been reported in epilepsy probands with a personal history of psychiatric disorders [15] and cognitive dysfunction or learning disability [16]. This evidence supports a common underlying pathophysiology between epilepsy and CNS comorbidities. While the association between other neurologic comorbidities and surgery outcomes remains to be investigated, additional evidence may suggest that the pathophysiology increases the probability that these individuals have a more generalized brain dysfunction or multifocal sites of seizure origin. If this association is true, children with a strong personal history of CNS comorbidities may be more likely to continue to have seizures after resective surgery.

The above studies have looked at individual associations between epilepsy and its comorbidities, family history and proband comorbidities, and proband comorbidities and surgery outcomes. However, there is no published literature describing the relationship between a family history of comorbidities and resective surgery outcomes. If family history is associated with surgery outcomes, this finding may modify the selection criteria for resective surgery and allow further personalization of prognostic assessment for patients. In addition, an association between family history information and surgery outcomes may provide insight regarding the etiology and natural history of epilepsy as well as a shared pathophysiological mechanism between epilepsy and its comorbidities.

The primary aim of this study was to determine prevalence of CNS comorbidities (ADHD, anxiety disorder, autism spectrum disorder, bipolar disorder, cognitive disability, depression, migraine, motor disability) in a) pediatric patients (probands) undergoing epilepsy surgery at a single institution and b) their families, and correlate these findings with long-term
seizure outcome. We hypothesized that certain CNS comorbidities in both probands and families would be associated with a poor long-term outcome.
METHODS

Standard protocol approvals, registrations, and patient consents. This study was approved by the Institutional Review Board at Cincinnati Children’s Hospital Medical Center (CCHMC) and the University of Cincinnati (Study #2013-2590). The continuation and maintenance of the clinical seizure database was approved by the Institutional Review Board at CCHMC (Study #2008-1043). Informed consent was obtained verbally from participants who completed telephone questionnaires and implied from participants who completed online questionnaires. Probands who were 18 or older at the time of this study were required to provide consent. The requirement for assent from probands under the age of 18, or probands who were 18 or older but remained under the legal guardianship of a parent, was waived. Documentation of written informed consent was waived for all individuals.

Cohort. This retrospective cross-sectional study compared family history of epilepsy and/or CNS comorbidities to surgery outcomes in pediatric patients who underwent resective brain surgery. Patients were identified through a clinical seizure database maintained by the CCHMC Division of Neurology. Patients qualified for surgery if they had failed to maintain good seizure control after a trial of at least two AEDs prior to surgery and a localized seizure focus was identified. All patients who underwent resective surgery for epilepsy, including hemispherectomy, lobectomy, and/or corticectomy, at CCHMC’s Comprehensive Epilepsy Center between January 1, 2007 and June 30, 2012 were contacted to obtain consent. Patients must have been under the age of 18 at the time of their surgery in order to qualify for this study. Children who underwent only palliative surgery, such as corpus callosotomy, were excluded.
**Family history information.** Family history information was collected via questionnaire from the patients’ parents or legal guardians, referred to as the “participants.” Participants who were not able to recount family history information or who did not speak English were excluded. Familial relationships were labeled in reference to the patient who received resective surgery, referred to as the “proband.”

Participants were recruited by mailed invitations to the home address on record. Nonrespondents were contacted by telephone calls after two weeks. Up to three voicemails were left for nonrespondents. Some participants received an additional written recruitment invitation at their child’s follow-up visit to Neurology or Neurosurgery.

An online questionnaire was developed to collect family history information using the Research Electronic Database Capture (REDCap) program (Appendix A). Participants had the option of taking the questionnaire online or via telephone with one of the researchers (KQ). A brief follow-up telephone interview was conducted with participants who took the questionnaire online to collect any needed additional information and allow participants to ask questions. The researcher was blind to proband surgery outcomes at the time of participant contacts.

The questionnaire elicited a three generation pedigree, including the proband and their parents, siblings, nieces, nephews, aunts, uncles, grandparents, and cousins. Participants were asked whether or not each identified family member had been diagnosed with any of the following health conditions: epilepsy, seizures not diagnosed as epilepsy, and CNS comorbidities including ADHD, anxiety disorder, autism spectrum disorder, bipolar disorder, cognitive disability, depression, migraine, and motor disability. Comorbidities were defined for participants as stated in Supplementary Table 1. For each individual reported to have seizures or epilepsy, participants were asked to report the age of seizure onset, type(s) of seizures
(convulsive, staring, and/or febrile), whether or not an individual had taken medication to treat seizures, and specific type of epilepsy. Comorbidities reported in the proband were verified as occurring pre-surgery or post-surgery in the electronic medical record. Demographic information about the probands, including age, sex, race, ethnicity, and adoptive status, and about the participants, including relationship to proband, age, sex, race, ethnicity, current state of residence, highest amount of education completed, employment status, and annual household income, was also collected in the questionnaire.

The proportion of affected individuals was calculated by the following formula: (# affected individuals)/(total # individuals). The proportion of affected probands, first degree relatives (FDRs), second degree relatives (SDRs), third degree relatives (TDRs), and total relatives was calculated for each individual comorbidity. FDRs included the proband, the proband’s parents, and full siblings. SDRs included the proband’s half siblings, nieces, nephews, aunts, uncles, and grandparents. TDRs included the proband’s first cousins, half aunts, and half uncles.

A history of epilepsy or seizures in family members was collapsed into a single variable, “epilepsy/seizures.” The proband was not included as a FDR when calculating the proportion of affected relatives with epilepsy/seizures. Comorbidity information was further collapsed into bins for some analyses. Comorbidities in the “Psychiatric” bin included one or more of the following: ADHD, anxiety disorder, bipolar disorder, and depression. Comorbidities in the “Other” bin included one or more of the following: autism spectrum disorder, cognitive disability, migraine, and motor disability. The “Any” bin included one or more of epilepsy/seizures and any of the comorbidities included in this study.
The proportion of affected probands, as reported by participants, was calculated for each individual comorbidity and bin. The proportion of probands affected with a comorbidity occurring pre-surgery, as verified by medical records, was calculated for each individual comorbidity. Probands with an un-verified comorbidity were treated as missing values for these calculations. General population rates of comorbidities are reported based on a literature review. General population rates of ADHD [4, 6], autism [17], cognitive disability [18-20] and motor disability [8, 21] are based on studies of pediatric populations, rates of anxiety disorder [22] and depression [23] are based on studies of adolescent and adult populations, and rates of bipolar disorder [10] and migraine [24, 25] are based on studies of adult populations.

**Surgery outcomes.** Additional information about the probands and their surgery outcomes was obtained from the clinical seizure database maintained by the CCHMC Division of Neurology. Data retrieved from the database included age, gender, seizure type and frequency, seizure etiology, diagnosis of tuberous sclerosis (TS), medication history, history of grid placement procedure, MRI imaging normality, seizure category, age at surgery, surgery type (temporal or extratemporal), surgery location, surgery pathology, and surgery outcome data (Appendix B).

Surgery outcome data were reported on a standardized six point scale, as defined by the International League Against Epilepsy (ILAE) [26]. Outcome data were reported at one year post-surgery and the patient’s most recent evaluation. Seizure category was defined based on brain magnetic resonance imaging (MRI) and electroencephalography (EEG) concordance with operated hemisphere. MRI was defined as either normal (which also included MRIs with only nonspecific findings), lesional unilateral (including neoplasm, focal cortical dysplasia, stroke, trauma or encephalitis), or lesional bilateral (including TS). Ictal EEG was defined as
lateralizing to left, right, or bilateral (including both multifocal bilateral independent ictal onset and bilateral/diffuse ictal onset). EEG was classified as either concordant (ictal EEG lateralized to operated hemisphere) or discordant (ictal EEG either contralateral to operated hemisphere, bilateral independent, or nonlateralizing). MRI/EEG concordance was defined as presence of a unilateral MRI lesion concordant with lateralized ictal EEG and operated hemisphere.

Outcome data were collapsed into dichotomous variables. Probands who remained seizure-free after surgery were categorized as ILAE = 1 and probands who were not seizure-free after surgery were categorized as ILAE > 1. Seizure category data were reported as an ordinal variable where 1 (best expected outcome) was defined as lesional or multi-lesional concordant, 2 was defined as non-lesional concordant, 3 was defined as lesional or multi-lesional discordant, and 4 (worst expected outcome) was defined as non-lesional discordant.

**Statistical analysis.** Descriptive statistics were used to report demographic information and the distribution of the collected data. Exact one-sided binomial analyses were performed for each comorbidity to determine if the proportion of affected probands was significantly greater than what would be expected based on prevalence rates in the general population. This was performed separately for participant-reported comorbidities and comorbidities verified by medical records. Mean proportions of affected FDRs, SDRs, TDRs and total relatives were calculated for all individual comorbidities and bins. Univariate analyses were performed to determine if the mean proportion of affected relatives across all probands was significantly greater than what would be expected based on prevalence rates in the general population.

Fisher’s exact tests were used to compare proband comorbidities to ILAE surgery outcomes and to compare seizure category across ILAE surgery outcomes. T-tests and Wilcoxon
rank sum analyses were used to compare the mean proportions of affected relatives to ILAE surgery outcomes. Logistic regression models were used to identify predictors of surgery outcome and seizure category. A stepwise variable selection procedure was used to find the most parsimonious model. Logistic regression models for both seizure outcome and seizure category included the following continuous variables: current age, age at surgery, age at most recent evaluation, time between surgery and most recent evaluation, and mean proportion of affected relatives, and the following categorical variables: proband comorbidities (presence or absence), diagnosis of TS (presence or absence), and surgery type (temporal or extratemporal), as covariates. All statistical analyses were performed using the SAS® statistical software package (version 9.3, SAS Institute Inc., Cary, NC).
RESULTS

Response rate and demographic information. One hundred and fifty-six individuals were contacted to participate in the study. Of these, eight individuals were excluded due to the inability to provide family history information (n=6) or the inability to speak English (n=2). A total of 52 participants completed the questionnaire, resulting in a 35.1% response rate (Appendix C). One individual was lost to follow-up regarding seizure outcome and proband comorbidity data. This individual was only included in the analysis of affected family members and demographic information.

There was an uneven distribution of males and females, with males making up 41.7% (10/24) of the ILAE = 1 group and 70.4% (19/27) of the ILAE > 1 group (p = 0.051) (Table 1). A greater proportion of probands in the ILAE > 1 group had a grid placement procedure than probands in the ILAE = 1 group (92.6% [25/27] v. 66.7% [16/24]; p = 0.033) (Supplementary Table 2). Probands in the ILAE > 1 group also had a greater number of medications tried during their treatment history than probands in the ILAE = 1 group (5.04 v. 3.38; p = 0.035) (Supplementary Table 2). No other significant differences were found in the demographic distribution of the two groups. (See Appendix D for expanded demographics.)

Comorbidities in probands. The sample population was further characterized by examining the proportion of affected probands and affected relatives for each of the comorbidities listed in the questionnaire. Probands in this sample had significantly higher rates of ADHD (p < 0.001), anxiety disorder (p = 0.004), autism spectrum disorder (p < 0.001), bipolar disorder (p = 0.041), cognitive disability (p < 0.001), depression (p < 0.001), and motor disability (p < 0.001) than the general population (Table 2).
**Comorbidities in probands’ families.** FDRs in this sample had significantly higher rates of ADHD (p < 0.001), autism (p = 0.20), depression (p = 0.001), and motor disability (p < 0.001) compared to the general population (Table 3). Total relatives had significantly higher rates of depression (p = 0.005), epilepsy/seizures (p = 0.026), and motor disability (p < 0.001) and a decreased prevalence of cognitive disability (p < 0.001) and migraine (p < 0.001) compared to the general population (Table 3). (See Appendix E for an expanded version of Table 3, including data on proportion of affected SDRs and TDRs.)

**Proband comorbidities as a predictor of surgery outcome.** The prevalence of comorbidities in probands and other relatives was compared to the probands’ ILAE outcome classification at their most recent follow-up evaluation. When looking at individual comorbidities, a diagnosis of autism or cognitive disability were significantly associated with an ILAE > 1 (Table 4). Nine of 51 probands (17.6%) were reported to have autism spectrum disorder. Eight of these individuals had an ILAE > 1 at their most recent follow-up evaluation (29.6% [8/27 probands with ILAE > 1]; p = 0.026). Forty of 51 probands (78.4%) were reported to have a cognitive disability. Twenty-five of these individuals had an ILAE > 1 at their most recent follow-up evaluation (92.6% [25/27 probands with ILAE > 1]; p = 0.015). Logistic regression models also found an association between cognitive disability and having an ILAE > 1, with the odds of a poor outcome increasing by a factor of 12.6 in probands diagnosed with a cognitive disability prior to surgery (OR = 12.6; 95% CIs 2.4 to 67.8; AUR = 0.722; p = 0.003) (data not shown). No other variables included in the logistic regression model were significant predictors of surgery outcome (data not shown).
When looking at bins of comorbidities, there was a significant association between probands reported to be affected with one or more comorbidities in the “Other” bin or reported to be affected with any of the examined comorbidities and an ILAE > 1 (Table 4). Forty-four of 51 probands (86.3%) were reported to have one or more comorbidities in the “Other” bin. Twenty-seven of these individuals had an ILAE > 1 at their most recent follow-up evaluation (100.0% [27/27 probands with ILAE > 1]; p = 0.003). Forty-six of 51 probands (90.2%) were reported to have one or more of any of the examined comorbidities. Twenty-seven of these individuals had an ILAE > 1 at their most recent follow-up evaluation (100.0% [27/27 probands with ILAE > 1]; p = 0.018). All of the unaffected probands in these bins had an ILAE = 1 at their most recent follow-up evaluation. When comparing the proportion of probands affected with individual comorbidities or bins based on ILAE scores after one year of follow-up, only the association between the probands being affected with any reported comorbidity and poor long-term seizure outcome remained (p = 0.0441) (Appendix F). When analyses were repeated comparing the prevalence of probands affected with pre-surgically diagnosed comorbidities across ILAE groups, the same significant associations were found as were reported for the participant-reported data (Appendices G & H).

**Family history of comorbidities as a predictor of surgery outcome.** An increased proportion of affected FDRs and total relatives with autism was significantly associated with an ILAE > 1 (p = 0.019, 0.037, respectively) (Table 5). Logistic regression models also demonstrated an association between proportion of affected FDRs with autism and ILAE > 1, with the odds of a poor outcome increasing by a factor of 2.6 for every 10% increase in proportion of affected FDRs, where the proband was included as a FDR (OR = 2.6; 95% CIs 1.0 to 6.9; Units = 0.10;
AUR = 0.632; p = 0.045). No other variables included in the logistic regression model were significant predictors of surgery outcome (data not shown). No associations were found when comparing the proportion of affected relatives with individual comorbidities or bins based on ILAE scores after one year of follow-up (data not shown).

**Comorbidities as a predictor of seizure category.** The prevalence of comorbidities in probands and other relatives was compared to the probands’ seizure category. Fisher’s exact tests demonstrated a significant difference in distribution of seizure category across ILAE groups, with more individuals with “poorer” (more discordant, MRI non-lesional) seizure category variables having an ILAE > 1 (p = 0.016) (Supplementary Table 2). Logistic regression models demonstrated an association between mean proportion of affected FDRs with one or more comorbidities in the “psychiatric” bin and “poorer” category, with the odds of having a “poorer” seizure category increasing by a factor of 1.4 for every 10% increase in proportion of affected FDRs (OR = 1.4; 95% CIs 1.0, 1.8; Units = 0.10; AUR = 0.656; p = 0.031) (data not shown). No other variables included in the logistic regression model were significant predictors of seizure category (data not shown).
DISCUSSION

This study is the first to comprehensively describe the relationships between the presence of CNS comorbidities in epilepsy probands, their families, and surgery outcomes. We identified higher rates of CNS comorbidities in both probands and their families. In addition, the presence of CNS comorbidities in probands and other family members was correlated with surgery outcome. The presence of autism or cognitive disability in probands and the presence of autism in FDRs were associated with poorer long-term seizure outcome following resective surgery. Our study findings support our original hypothesis and add to evidence in favor of a common heritability and pathophysiological mechanism between epilepsy and its CNS comorbidities.

Comorbidities in probands. Epilepsy probands had significantly higher rates of ADHD, anxiety disorder, autism spectrum disorder, bipolar disorder, cognitive disability, depression and motor disability than the general population, but not of migraine. In our population, the rates of many comorbidities fell within the range of the rates previously reported for the epilepsy population (Supplementary Table 3). However, there were subtle differences in our population compared to those reported in the literature, including lower rates of bipolar disorder (3.9% v. 12%) and higher rates of cognitive and motor disability (78.4% & 39.2%, respectively v. 15-30% for either comorbidity). These differences may be due to differences in population characteristics or study design. For example, the prevalence rates for bipolar disorder and migraine have only been reported in adult populations with epilepsy [5, 6, 10, 12]. These comorbidities may be under diagnosed in children or pediatric probands may not have developed them yet, which may explain the discrepancy between our rates and those reported in adult populations. Regarding study design, our questionnaire used a broad definition of cognitive
disability and motor disability (Supplementary Table 1), including intellectual disabilities, developmental delays and learning delays in our classification of cognitive disability. This may partially explain the large percentage (78.4) of patients affected with cognitive disability in our sample. In addition, our sample population includes only patients with intractable epilepsy. Longer duration of refractory epilepsy has been previously associated with cognitive deterioration in probands [27], suggesting that disease progression may also partially account for the higher prevalence of cognitive impairment on our population.

**Comorbidities in probands’ families.** Probands’ family members also had higher rates of several of the examined comorbidities compared to the general population. Specifically, there were increased rates of FDRs affected with ADHD, autism spectrum disorder, depression, and motor disability. There were increased rates of total relatives affected with depression, epilepsy/seizures, and motor disability. However, the rates of cognitive disability and migraines in total relatives were significantly lower than the reported general population rates for these conditions. This discrepancy may be partially due to the fact that the population of an individual’s total relatives includes both children and adults. Relatives in different age groups have had a varying amount of time to develop comorbidities, which may skew the results. In addition, self-reported data are known to be limited by recall bias [28]. However, studies have consistently found family history information to have a high specificity, meaning few relatives without disease are misclassified as having disease, but lower sensitivity, meaning relatives with disease are more likely to be misclassified as disease-free [29]. The accuracy of family history information may also be affected by other characteristics of the informant or their relatives. For example, previous studies have shown that the sensitivity of reported health information
decreases as the degree of relatedness increases [30]. Therefore, we suspect that the true prevalence rates of comorbidities in our study are higher than the rates that were reported by participants, particularly for more distant relatives.

This is the first study to investigate the prevalence rates of comorbidities in epilepsy probands’ other family members. Our results suggest that additional family members may also be at risk for developing CNS comorbidities over their lifetime, emphasizing the importance of collecting family history information for clinicians. Replication of these findings in a large population will elucidate whether an increased rate of comorbidities in family members is true for the general epilepsy population or may be more specific to those with intractable epilepsy. Our analyses included the proband as a FDR for all comorbidities except for epilepsy/seizures. It is possible that including the proband in these analyses may bias the results towards significance in light of the known association between higher rates of comorbidities among probands. However, removing the proband from the family history analyses would result in an incomplete portrait of the families’ medical history. Since family history information is often analyzed as a whole in a clinical setting, the inclusion of the proband more closely mirrors current clinical practice.

**Proband comorbidities as a predictor of surgery outcome.** When comparing the presence of individual comorbidities in probands to their ILAE classification post-surgery, probands with autism or cognitive disabilities were more likely to have poor long-term seizure outcome. Probands reported to be affected with one or more comorbidities in the “Other” bin and probands reported to be affected with any of the examined comorbidities were also more likely to have
poor long-term seizure outcome. Strikingly, all probands who were unaffected by these bins of comorbidities had remained seizure-free at their most recent evaluation.

The questionnaire was designed to assess the presence of comorbidities in probands, but not the time of diagnosis. This limits our ability to assess whether the comorbidities occurred prior to, or were a result of the surgery. However, data analysis revealed the same significant associations between the presence of cognitive disability and autism and worse surgery outcomes when the reported comorbidities were verified as occurring pre-surgery by medical records. Not only was the presence of cognitive disability in probands highly associated with their surgery outcomes in a cross-sectional analysis, but the correlation remained when the analysis was restricted to only pre-surgical diagnoses. Taken as a whole, these data imply that the presence of cognitive disability or autism in a proband with epilepsy has a negative impact on clinical outcome of resective surgery.

Previous relationships have been reported in the literature between worse surgery outcomes and cognitive dysfunction [16] and a lifetime history psychiatric comorbidities [15] in probands. The finding of cognitive disability as a predictor of worse surgery outcomes in our population further supports the importance of this diagnosis when considering resective surgery prognosis. However, our study did not replicate the reported association with individual or pooled psychiatric comorbidities. This discrepancy may be explained via differences in study populations. While Kanner et al. [15] reported on a lifetime history of psychiatric comorbidities in their probands, which is similar to our participant-reported data, their patient population consisted of adults with epilepsy as compared to our pediatric population. As our population ages, the rate of psychiatric comorbidities may increase. Our findings support the importance of proband comorbid conditions as potential predictors of surgery outcome; however, more studies
are needed to further characterize such associations in different subsets of the epilepsy population.

**Family history of comorbidities as a predictor of surgery outcome.** When comparing the rates of comorbidities in other family members to probands’ surgery outcomes, the proportion of affected FDRs and total relatives with autism was significantly associated with worse surgery outcomes at the most recent follow-up evaluation. This evidence supports that family history information can add to a proband’s clinical picture and provide the clinician with additional information to use in his or her prognostic assessment [31]. Since no other studies have investigated the relationship between family history of comorbidities and surgery outcomes, future studies are needed to further characterize the associations in other sample populations.

**Comorbidities as a predictor of seizure category.** Our data showed a significant difference in the distribution of seizure category (a measure of concordance between MRI, ictal EEG and operated hemisphere) between the two ILAE groups, with more individuals with “poorer” (more discordant, MRI non-lesional) seizure categories having worse surgery outcomes. The proportion of affected FDRs with one or more comorbidities in the “psychiatric” bin was significantly associated with having a “poorer” seizure category. This finding suggests that families with a higher prevalence of psychiatric comorbidities are associated with epilepsy that is more likely to persist after a focal resection. Two possible general hypotheses could be drawn. The first is that these patients are more likely to have a widely distributed epileptic network that is difficult to completely localize and resect. The second is that certain patients with a genetic propensity to
other brain disorders have localizable epilepsy which is resected completely, but a secondary area of epileptogenesis develops which prevents them from being seizure free long-term.

The relationship between autism, cognitive impairment and the evolution of poor seizure outcomes over time supports our study’s hypothesis. The fact that initial postoperative outcomes at one year were generally favorable in these patients, and then deteriorated to significantly poorer outcomes, suggests epileptogenesis at another site rather than incomplete resection of the epileptic network at the time of surgery. Seizures resulting from incomplete resection of the epileptic network rather than secondary epileptogenesis are generally present within 6-12 months of epilepsy surgery [32]. The current study supports the hypothesis for a common pathophysiology between epilepsy and its CNS comorbidities and a shared genetic component contributing to an as yet unknown mechanism of brain dysfunction. Further studies are needed to examine these hypotheses.

**Study limitations.** Although our study was limited to those who chose to participate, our study population was similar to the larger CCHMC epilepsy population in terms of the relative frequency of seizure free outcome and the distribution between seizure category and outcome. The majority of patients had a histopathological diagnosis of cortical dysplasia as an etiology. This is the most common cause of pediatric intractable epilepsy leading to epilepsy surgery [33]; however this does limit the generalizability to other etiologies. We cannot eliminate the possibility of recall and misclassification bias in the family history data, as discussed above. However, despite these biases towards the null hypothesis, the significance of cognitive disability and autism as important factors in our population continues to emerge as robust findings.
Conclusions. Our study findings represent a variety of novel and replicated associations, with our results both supporting and adding to the current literature. The increased prevalence of CNS comorbidities in epilepsy probands is consistent with reported literature on epilepsy comorbidities, although this has not been previously investigated in pediatric patients undergoing epilepsy surgery. The increased prevalence of these comorbidities in other family members is a novel association that contributes to the support for a common heritability between epilepsy and its comorbidities. Our study contributes to the small body of literature that has considered the relationship between comorbidities and proband surgery outcomes. Cognitive disability and autism spectrum disorder appear to be important proband factors in surgery prognosis, and the association between autism and surgery outcome strengthens with the addition of other family members. All of these findings support the hypothesis of a common pathophysiological mechanism between epilepsy and its comorbidities and highlight the importance of these comorbidities in both the proband and other relatives. Further research is needed to replicate our associations and investigate the potential underlying mechanisms, which may lead to new diagnostic and therapeutic targets.
REFERENCES


## Table 1  Proband & Participant Demographics

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<th>Proband Demographics</th>
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<td>ILAE = 1</td>
<td>ILAE &gt; 1</td>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<td>13.5 years</td>
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<td>5.5</td>
<td>13.0 years</td>
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<tr>
<td>Mean time from surgery to most recent evaluation&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>44.7 months</td>
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<td>41.0 months</td>
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<tr>
<td>Total number of CNS comorbidities&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1.7</td>
<td>2.5</td>
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<td>Gender&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (41.7)</td>
<td>19 (70.4)</td>
<td>30 (57.7)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (58.3)</td>
<td>8 (29.6)</td>
<td>22 (42.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>23 (95.8)</td>
<td>26 (96.3)</td>
<td>49 (94.2)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (4.2)</td>
<td>1 (3.7)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Legal guardianship status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0-17, parent has legal guardianship</td>
<td>18 (75.0)</td>
<td>20 (74.1)</td>
<td>38 (73.1)</td>
</tr>
<tr>
<td>Age 18+, parent does not have guardianship</td>
<td>4 (16.7)</td>
<td>5 (18.5)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Age 18+, parent has legal guardianship</td>
<td>2 (8.3)</td>
<td>1 (3.7)</td>
<td>3 (5.8)</td>
</tr>
</tbody>
</table>

## Participant Demographics

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>40.8 years</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>23 (95.8)</td>
<td>25 (92.3)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (4.2)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Relationship to proband</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>1 (4.2)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Mother</td>
<td>23 (95.8)</td>
<td>23 (85.2)</td>
</tr>
<tr>
<td>State of Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohio</td>
<td>14 (58.3)</td>
<td>14 (51.9)</td>
</tr>
</tbody>
</table>
ILAE outcomes are based on most recent clinical evaluation
For ILAE = 1, n = 24; For ILAE > 1, n = 27; Total N = 52
Data collected from questionnaire, unless otherwise specified
a) Data collected from clinical database maintained by CCHMC Department of Neurology
b) N = 51
c) Significant difference in distribution between ILAE groups by Fisher’s exact test, p=0.051
Abbreviations: ILAE = International League Against Epilepsy

<table>
<thead>
<tr>
<th>Location</th>
<th>ILAE = 1</th>
<th>ILAE &gt; 1</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kentucky</td>
<td>4 (16.7)</td>
<td>5 (18.5)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Indiana</td>
<td>3 (12.5)</td>
<td>3 (11.1)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (12.5)</td>
<td>5 (18.5)</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>Measure</td>
<td>n (%)</td>
<td>General population rates (%)</td>
<td>p Value</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------</td>
<td>------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>ADHD</td>
<td>15 (29.4)</td>
<td>4.0\textsuperscript{4,6}</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11 (21.6)</td>
<td>10.0\textsuperscript{23}</td>
<td>0.004</td>
</tr>
<tr>
<td>Autism</td>
<td>9 (17.6)</td>
<td>1.1\textsuperscript{24}</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>2 (3.9)</td>
<td>1.5\textsuperscript{10}</td>
<td>0.041</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>40 (78.4)</td>
<td>21.1\textsuperscript{25-27}</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (19.6)</td>
<td>5.4\textsuperscript{28}</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Migraine</td>
<td>9 (17.6)</td>
<td>16.6\textsuperscript{29,30}</td>
<td>0.335</td>
</tr>
<tr>
<td>Motor disability</td>
<td>20 (39.2)</td>
<td>0.8\textsuperscript{8,31}</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

p Values from exact one-sided binomial model; N = 51
Percentages calculated by multiplying the proportion of affected probands by 100
General population rates were reported from the following sources: ADHD – [4, 6]; anxiety – [22]; autism – [17]; bipolar disorder – [10]; cognitive disability – [18-20]; depression – [23]; migraine – [24, 25]; motor disability – [8, 21];
Abbreviations: ADHD = attention deficit hyperactivity disorder
<table>
<thead>
<tr>
<th>Measure</th>
<th>FDRs</th>
<th>Total relatives</th>
<th>General population rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>ADHD</td>
<td>0.112</td>
<td>0.129</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.104</td>
<td>0.180</td>
<td>0.878</td>
</tr>
<tr>
<td>Autism</td>
<td>0.046</td>
<td>0.106</td>
<td>0.020</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0.029</td>
<td>0.085</td>
<td>0.226</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>0.207</td>
<td>0.135</td>
<td>0.843</td>
</tr>
<tr>
<td>Depression</td>
<td>0.170</td>
<td>0.239</td>
<td>0.001</td>
</tr>
<tr>
<td>Epilepsy/seizures</td>
<td>0.032</td>
<td>0.091</td>
<td>0.085</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.157</td>
<td>0.221</td>
<td>0.771</td>
</tr>
<tr>
<td>Motor disability</td>
<td>0.096</td>
<td>0.127</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

p Values from univariate analysis; N = 52 families


Abbreviation: FDRs = first degree relatives, including the proband, the proband’s parents, and full siblings; The proband was not included as a FDR when calculating the proportion of affected relatives with epilepsy/seizures; ADHD = attention deficit hyperactivity disorder; SD = standard deviation
<table>
<thead>
<tr>
<th>Measure</th>
<th>ILAE = 1 (n = 24)</th>
<th>ILAE &gt; 1 (n = 27)</th>
<th>Total Affected (N = 51)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC (bin)</td>
<td>9 (37.5)</td>
<td>13 (48.1)</td>
<td>22 (43.1)</td>
<td>0.573</td>
</tr>
<tr>
<td>OTH (bin)</td>
<td>17 (70.8)</td>
<td>27 (100.0)</td>
<td>44 (86.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>ANY (bin)</td>
<td>19 (79.2)</td>
<td>27 (100.0)</td>
<td>46 (90.2)</td>
<td>0.018</td>
</tr>
<tr>
<td>ADHD</td>
<td>6 (25.0)</td>
<td>10 (37.0)</td>
<td>16 (31.4)</td>
<td>0.385</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (16.7)</td>
<td>8 (29.6)</td>
<td>12 (23.5)</td>
<td>0.335</td>
</tr>
<tr>
<td>Autism</td>
<td>1 (4.2)</td>
<td>8 (29.6)</td>
<td>9 (17.6)</td>
<td>0.026</td>
</tr>
<tr>
<td>Bipolar</td>
<td>1 (4.2)</td>
<td>2 (7.4)</td>
<td>3 (5.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>15 (62.5)</td>
<td>25 (92.6)</td>
<td>40 (78.4)</td>
<td>0.015</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (16.7)</td>
<td>7 (25.9)</td>
<td>11 (21.6)</td>
<td>0.508</td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (20.8)</td>
<td>5 (18.5)</td>
<td>10 (19.6)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Motor disability</strong></td>
<td>12 (50.0)</td>
<td>8 (29.6)</td>
<td>20 (39.2)</td>
<td>0.161</td>
</tr>
</tbody>
</table>

p Values from Fisher's exact test; N = 51
ILAE outcomes are based on most recent clinical evaluation;
Percentages calculated by multiplying the proportion of affected probands by 100
Abbreviations: ILAE = International League Against Epilepsy; PSC = Psychiatric comorbidities (ADHD, anxiety, bipolar disorder, depression); OTH = Other CNS comorbidities (autism, cognitive disability, migraine, motor disability); ANY (bin) = any comorbidities (ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression, epilepsy/seizures, migraine, motor disability); ADHD = attention deficit hyperactivity disorder
Table 5  Mean proportion of affected relatives v. ILAE outcomes for individual comorbidities

<table>
<thead>
<tr>
<th>Measure</th>
<th>FDRs</th>
<th>Total relatives</th>
<th>p Value</th>
<th>FDRs</th>
<th>Total relatives</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ILAE = 1</td>
<td>ILAE &gt; 1</td>
<td></td>
<td>ILAE = 1</td>
<td>ILAE &gt; 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PSC (bin)</td>
<td>0.247</td>
<td>0.265</td>
<td>0.259</td>
<td>0.212</td>
<td>0.491</td>
<td>0.139</td>
</tr>
<tr>
<td>OTH (bin)</td>
<td>0.299</td>
<td>0.203</td>
<td>0.380</td>
<td>0.179</td>
<td>0.143</td>
<td>0.111</td>
</tr>
<tr>
<td>ANY (bin)</td>
<td>0.449</td>
<td>0.247</td>
<td>0.478</td>
<td>0.237</td>
<td>0.671</td>
<td>0.221</td>
</tr>
<tr>
<td>ADHD</td>
<td>0.108</td>
<td>0.125</td>
<td>0.113</td>
<td>0.135</td>
<td>0.901</td>
<td>0.046</td>
</tr>
<tr>
<td>Autism</td>
<td>0.086</td>
<td>0.180</td>
<td>0.116</td>
<td>0.184</td>
<td>0.406</td>
<td>0.058</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0.031</td>
<td>0.088</td>
<td>0.029</td>
<td>0.086</td>
<td>0.907</td>
<td>0.020</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>0.180</td>
<td>0.163</td>
<td>0.239</td>
<td>0.094</td>
<td>0.154</td>
<td>0.051</td>
</tr>
<tr>
<td>Depression</td>
<td>0.156</td>
<td>0.279</td>
<td>0.182</td>
<td>0.207</td>
<td>0.240</td>
<td>0.076</td>
</tr>
<tr>
<td>Epilepsy/seizures</td>
<td>0.083</td>
<td>0.202</td>
<td>0.148</td>
<td>0.362</td>
<td>0.451</td>
<td>0.292</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.157</td>
<td>0.218</td>
<td>0.162</td>
<td>0.229</td>
<td>1.000</td>
<td>0.069</td>
</tr>
<tr>
<td>Motor disability</td>
<td>0.118</td>
<td>0.126</td>
<td>0.080</td>
<td>0.129</td>
<td>0.292</td>
<td>0.031</td>
</tr>
</tbody>
</table>

p Values from Wilcoxon rank sum analyses
ILAE outcomes are based on most recent clinical evaluation
For ILAE = 1, n = 24 families; For ILAE > 1, n = 27 families; Total N = 51 families
Abbreviation: ILAE = International League Against Epilepsy; FDRs = first degree relatives, including the proband, the proband’s parents, and full siblings; The proband was not included as a FDR when calculating the proportion of affected relatives with epilepsy/seizures; PSC = Psychiatric comorbidities (ADHD, anxiety, bipolar disorder, depression); OTH = Other neurologic comorbidities (autism, cognitive disability, migraine, motor disability); ANY (bin) = any comorbidities (ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression, epilepsy/seizures, migraine, motor disability); ADHD = attention deficit hyperactivity disorder; SD = standard deviation
### SUPPLEMENTARY TABLES

#### Supplementary Table 1  Comorbidity definitions used in questionnaire

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Questionnaire Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD/ADHD</td>
<td>Problems with attention, hyperactivity or impulsiveness</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>Feelings of worry, uneasiness or fear of uncertain events</td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>Problems with social interaction and communication skills</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Severe mood swings, often between an excited and depressed state</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>Problems with learning, language or social skills, including developmental delays and learning delays</td>
</tr>
<tr>
<td>Depression</td>
<td>Feelings of sadness, anxiety, hopelessness or worry</td>
</tr>
<tr>
<td>Migraine</td>
<td>Severe headaches that can include nausea and vision problems</td>
</tr>
<tr>
<td>Motor disability</td>
<td>Problems with muscle movements, muscle control or posture</td>
</tr>
</tbody>
</table>

Abbreviations: ADD/ADHD = attention deficit disorder/attention deficit hyperactivity disorder
<table>
<thead>
<tr>
<th></th>
<th>ILAE = 1 (n = 24)</th>
<th>ILAE &gt; 1 (n = 27)</th>
<th>Total (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Total number of medications tried&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.38</td>
<td>2.7</td>
<td>5.04</td>
</tr>
<tr>
<td>Diagnosis of TS</td>
<td>4 (16.7)</td>
<td>7 (25.9)</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>Grid placement&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (66.7)</td>
<td>25 (92.6)</td>
<td>42 (80.8)</td>
</tr>
<tr>
<td>Seizure category&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesional or multi-lesional concordant</td>
<td>16 (66.7)</td>
<td>12 (44.4)</td>
<td>29 (55.8)</td>
</tr>
<tr>
<td>Non-lesional concordant</td>
<td>5 (20.8)</td>
<td>1 (3.7)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Lesional or multi-lesional discordant</td>
<td>2 (8.3)</td>
<td>9 (33.3)</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Non-lesional discordant</td>
<td>1 (4.2)</td>
<td>5 (18.5)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Surgery Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>4 (16.7)</td>
<td>6 (22.2)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Extratemporal</td>
<td>20 (83.3)</td>
<td>21 (77.8)</td>
<td>42 (80.8)</td>
</tr>
</tbody>
</table>

ILAE outcomes are based on most recent clinical evaluation
Data collected from clinical database maintained by CCHMC Department of Neurology
a) Significant difference in distribution between ILAE groups by Fisher’s exact test, p = 0.033
b) Significant difference in distribution between ILAE groups by t-test and Wilcoxon rank sum analysis, p = 0.033, 0.035, respectively
c) Significant difference in distribution between ILAE groups by Fisher’s exact test, p = 0.016
Abbreviations: ILAE = International League Against Epilepsy; TS = Tuberous sclerosis; SD = standard deviation
<table>
<thead>
<tr>
<th>Measure</th>
<th>% Affected (Our study)</th>
<th>% Affected (Literature)</th>
<th>Literature Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>29.4</td>
<td>8-77</td>
<td>Children with epilepsy</td>
</tr>
<tr>
<td>Anxiety</td>
<td>21.6</td>
<td>16</td>
<td>Children with epilepsy</td>
</tr>
<tr>
<td>Autism</td>
<td>17.6</td>
<td>*14 (42/301)</td>
<td>Children with autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>had epilepsy</td>
</tr>
<tr>
<td>Bipolar</td>
<td>3.9</td>
<td>12</td>
<td>Adults with epilepsy</td>
</tr>
<tr>
<td>Cognitive Disability</td>
<td>78.4</td>
<td>15-30</td>
<td>Individuals with childhood-onset epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cognitive and/or motor disability</td>
</tr>
<tr>
<td>Motor Disability</td>
<td>39.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>19.6</td>
<td>26</td>
<td>Children with epilepsy</td>
</tr>
<tr>
<td>Migraine</td>
<td>17.6</td>
<td>20-24</td>
<td>Adults with epilepsy</td>
</tr>
</tbody>
</table>

N = 51

Percentages calculated by multiplying the proportion of affected probands by 100

Literature rates were reported from the following sources: ADHD – [4, 6]; anxiety – [6]; autism – [6]; bipolar disorder – [10]; cognitive and motor disability – [8]; depression – [6]; migraine – [6];


Abbreviations: ADHD = attention deficit hyperactivity disorder
Appendix A: Online Survey Questions

Survey Instructions

Thank you for agreeing to participate in this research study! Instructions: Please answer the questions in this survey about your child’s blood relatives. This includes brothers and sisters, parents, aunts, uncles, cousins and grandparents. In this survey, you will be asked to list family members and whether or not each person has epilepsy, seizures, or related medical conditions such as migraine, cognitive disabilities, motor disabilities, autism spectrum disorder, depression, anxiety disorder, bipolar disorder or ADHD. Do not include information about family members not related by blood. For adoptive and foster parents and legal guardians: Please answer the questions in this survey about your child’s blood relatives. If you do not have information about your child’s blood relatives, you are not eligible to participate in this research study. Following the completion of the survey: We will schedule a follow-up phone call with you to confirm the information you provide and to answer any questions you have. If your child is currently age 18 or older, we will need to contact your son or daughter directly to ask for their permission to link your survey answers with information from his or her medical records. We will ask for the best way to contact your son or daughter during the follow-up phone call if we have not already.

Please enter the three digit identification number located at the top of the survey invitation you received in the mail.

Survey Eligibility

Has your child received epilepsy surgery at Cincinnati Children’s Hospital (CCHMC)’s Comprehensive Epilepsy Center?

☐ Yes
☐ No

**If “No”: End Survey.

Is your child who received epilepsy surgery currently 18 years of age or older? (If your child is 18 years of age or older, he/she will need to give the researchers permission to look at his/her medical records.)

☐ Yes, my child is 18 years of age or older
☐ No, my child is 17 years of age or younger
☐ No, my child has passed away

**If “Yes, my child is 18 years of age or older” is indicated:

Does your child have a cognitive disability that results in you remaining as his/her legal guardian?

☐ Yes
☐ No

(All participants continue)

Please answer the following questions about yourself.

What is your relationship to the child who received epilepsy surgery at CCHMC’s Comprehensive Epilepsy Center?

☐ Biological Parent
☐ Step-Parent
☐ Adoptive Parent
☐ Foster Parent
☐ Legal Guardian
**If any response except “Biological Parent” is indicated:**
Are you able to answer questions about this child's family members, such as whether or not they have been diagnosed with epilepsy or other health conditions?

☐ Yes  
☐ No

**If “No”: End Survey**

What is your age in years?  
(Drop Down Menu)

What is your sex?

☐ Male  
☐ Female

What is your race? Check all that apply:

☐ American Indian or Alaska Native  
☐ Asian  
☐ Black or African American  
☐ Native Hawaiian or Pacific Islander  
☐ White  
☐ Other

If other, please specify:

________________________________________

What is your ethnicity?

☐ Hispanic  
☐ Non-Hispanic

What is the highest amount of schooling you have completed?

☐ Less than high school  
☐ Some high school  
☐ Some college or technical school  
☐ Two year college or technical school degree  
☐ Four year college degree  
☐ Some graduate school  
☐ Graduate or advanced degree

Are you currently employed outside of your home?

☐ Yes, full-time  
☐ Yes, part-time  
☐ No, I work from home  
☐ No, I am not currently employed  
☐ Prefer not to answer
What is your annual household income?

☐ Less than $10,000
☐ $10,000 to less than $20,000
☐ $20,000 to less than $30,000
☐ $30,000 to less than $40,000
☐ $40,000 to less than $50,000
☐ $50,000 to less than $60,000
☐ $60,000 to less than $70,000
☐ $70,000 to less than $80,000
☐ $80,000 to less than $90,000
☐ $90,000 to less than $100,000
☐ $100,000 or greater
☐ Prefer not to answer

In what state do you currently live?
(Drop Down Menu)

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Please answer the following questions about the child who received epilepsy surgery at CCHMC's Comprehensive Epilepsy Center.

**Depending on answer to Survey Eligibility question “Is your child who received epilepsy surgery currently 18 years of age or older?”:

What is this child's age in years? OR What was this child's age in years when he/she died?
(Drop Down Menu-**If Response 1 or 2) (Drop Down Menu-**If Response 3)

Was this child adopted?

☐ Yes
☐ No

**If “Yes”:
Are you able to answer questions about this child's family members, such as whether or not they have been diagnosed with epilepsy or other health conditions?

☐ Yes
☐ No

**If “No”: End Survey.

(All participants continue)

What is this child's sex?

☐ Male
☐ Female
What is this child’s race? Check all that apply:

☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Pacific Islander
☐ White
☐ Other

If other, please specify:

____________________________________

What is this child’s ethnicity?

☐ Hispanic
☐ Non-Hispanic

Is this child a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this child ever been told by a healthcare professional that he/she has any of the following? Check all that apply:

☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don't Know

How many children does this person have?

☐ 0
☐ 1
☐ 2
☐ 3
☐ More than 3

**QUESTION BLOCK: CHILDREN**

**If any response except “0” is indicated:**
Please answer the following questions about this person's FIRST CHILD.

What is this child's sex?

☐ Male
☐ Female

Is this person still living?

☐ Yes
☐ No

What is this person's current age in years or the age he/she passed away?
(Drop Down Menu)

Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that he/she has any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when he/she started having seizures?
(Drop Down Menu)
What type(s) of seizures does/did this person have? Check all that apply:

- Staring seizures
- Convulsive seizures (jerking seizures)
- Febrile seizures (seizures with fever)
- Don't Know

Has this person ever taken medication to treat his/her seizures?

- Yes
- No
- Don't Know

**Repeat QUESTION BLOCK: CHILDREN for UP TO THREE CHILDREN**

**If “More than 3” is indicated:**

We apologize but there is not enough space provided to enter health information for this person's additional children. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants continue)

Please answer the following questions about your child's brothers and sisters.

How many full or half brothers does your child have?

- 0
- 1
- 2
- 3
- 4
- 5
- More than 5

How many full or half sisters does your child have?

- 0
- 1
- 2
- 3
- 4
- 5
- More than 5

Please answer the following questions about your child's brothers.

**If “0” brothers is indicated:**

You have indicated that your child has no full or half brothers. Please continue to the next page.

QUESTION BLOCK: BROTHERS

**If any response except “0” brothers is indicated:**
Please answer the following questions about your child’s FIRST BROTHER.

For your child’s first brother, is he a full sibling or half sibling to your child?

☐ Full sibling
☐ Half sibling through the child’s father
☐ Half sibling through the child’s mother

Is this person still living?

☐ Yes
☐ No

What is this person’s current age in years or the age he passed away?
(Drop Down Menu)

Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that he has any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don’t Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren’t sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when he started having seizures?
(Drop Down Menu)
What type(s) of seizures does/did this person have? Check all that apply:

- [ ] Staring seizures
- [ ] Convulsive seizures (jerking seizures)
- [ ] Febrile seizures (seizures with fever)
- [ ] Don't Know

Has this person ever taken medication to treat his seizures?

- [ ] Yes
- [ ] No
- [ ] Don't Know

(All participants continue.)

How many children does this person have?

- [ ] 0
- [ ] 1
- [ ] 2
- [ ] 3
- [ ] More than 3

**If any response except “0” is indicated, repeat QUESTION BLOCK: CHILDREN for UP TO THREE CHILDREN**

**If “More than 3” is indicated:**
We apologize but there is not enough space provided to enter health information for this person's additional children. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants continue)

**Repeat QUESTION BLOCK: BROTHERS for UP TO FIVE BROTHERS**

**If “More than 5” brothers is indicated:**
We apologize but there is not enough space provided to enter health information for your child's additional brothers. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants continue)

Please answer the following questions about your child's sisters.

**If “0” sisters is indicated:**
You have indicated that your child has no full or half sisters. Please continue to the next page.

QUESTION BLOCK: SISTERS

**If any response except “0” sisters is indicated:
Please answer the following questions about your child's FIRST SISTER.

For your child's first sister, is she a full sibling or half sibling to your child?

- [ ] Full sibling
- [ ] Half sibling through the child's father
- [ ] Half sibling through the child's mother

Is this person still living?

- [ ] Yes
- [ ] No

What is this person's current age in years or the age she passed away?
(Drop Down Menu)

Is this person a twin?

- [ ] No
- [ ] Yes - Identical (Same)
- [ ] Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that she has any of the following? Check all that apply:

- [ ] Epilepsy
- [ ] Seizures (not diagnosed as epilepsy)
- [ ] Migraine (severe headaches that can include nausea and vision problems)
- [ ] Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- [ ] Motor disability (problems with muscle movements, muscle control or posture)
- [ ] Autism spectrum disorder (problems with social interaction and communication skills)
- [ ] Depression (feelings of sadness, anxiety, hopelessness or worry)
- [ ] Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- [ ] Bipolar disorder (severe mood swings, often between an excited and depressed state)
- [ ] ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- [ ] None of the above
- [ ] Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state "unknown")

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when she started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

- [ ] Staring seizures
- [ ] Convulsive seizures (jerking seizures)
- [ ] Febrile seizures (seizures with fever)
- [ ] Don't Know
Has this person ever taken medication to treat her seizures?

☐ Yes
☐ No
☐ Don’t Know

(All participants continue)

How many children does this person have?

☐ 0
☐ 1
☐ 2
☐ 3
☐ More than 3

**If any response except “0” is indicated, repeat QUESTION BLOCK: CHILDREN for UP TO THREE CHILDREN**

**If “More than 3” is indicated:
We apologize but there is not enough space provided to enter health information for this person's additional children. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants continue)

**Repeat QUESTION BLOCK: SISTERS for UP TO FIVE SISTERS**

**If “More than 5” sisters is indicated:
We apologize but there is not enough space provided to enter health information for your child's additional sisters. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants continue)

Please answer the following questions about your child's parents.

Please answer the following questions about your child's FATHER.

Is this person still living?

☐ Yes
☐ No

What is this person's current age in years or the age he passed away?

(Drop Down Menu)
Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that he has any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

*(If no specific diagnosis was given or if you aren't sure, please state “unknown”)*

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when he started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

☐ Staring seizures
☐ Convulsive seizures (jerking seizures)
☐ Febrile seizures (seizures with fever)
☐ Don't Know

Has this person ever taken medication to treat his seizures?

☐ Yes
☐ No
☐ Don't Know

(All participants continue)

What is the ethnic background or country(ies) of origin for the father’s family? (Example: Irish, Italian, German, Eastern Indian or Chinese, etc.) Include one or more if known. If unknown, state “unknown.”

________________________
Are you able to answer questions about the child's father's family members, such as whether or not they have been diagnosed with epilepsy or other health conditions?

☐ Yes
☐ No

If no, please state why:

______________________________

Please answer the following questions about your child's MOTHER.

Is this person still living?

☐ Yes
☐ No

What is this person's current age in years or the age she passed away?
(Drop Down Menu)

Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that she has any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when she started having seizures?
(Drop Down Menu)
What type(s) of seizures does/did this person have? Check all that apply:

☐ Staring seizures
☐ Convulsive seizures (jerking seizures)
☐ Febrile seizures (seizures with fever)
☐ Don’t Know

Has this person ever taken medication to treat her seizures?

☐ Yes
☐ No
☐ Don’t Know

(All participants continue)

What is the ethnic background or country(ies) of origin for the mother’s family? (Example: Irish, Italian, German, Eastern Indian or Chinese, etc.) Include one or more if known. If unknown, state “unknown.”

_____________________

Are you able to answer questions about the child’s mother’s family members, such as whether or not they have been diagnosed with epilepsy or other health conditions?

☐ Yes
☐ No

If no, please state why:

_____________________

Is there any chance that the child's parents are related by blood?

☐ Yes
☐ No
☐ Don’t Know

Please answer the following questions about your child's FATHER'S SISTERS AND BROTHERS (paternal aunts and uncles).

**If “No” is indicated to “Are you able to answer questions about the child’s father’s family members...”:
You have indicated that you do not have information about your child's father's family. Please continue to the next page.

(All participants in this section continue)
How many full or half brothers and sisters does your child's father have?

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ More than 5

**If “0” is indicated:**
You have indicated that your child's father has no full or half siblings. Please continue to the next page.

**QUESTION BLOCK: FATHER’S SIBLINGS**

**If any response except “0” full or half brothers and sisters is indicated:**
Please answer the following questions about your child's FATHER'S FIRST SIBLING.

For the father's first sibling, is he/she a full sibling or half sibling to the father?

☐ Full sibling
☐ Half sibling through the his father
☐ Half sibling through his mother

Is this person still living?

☐ Yes
☐ No

What is this person's sex?

☐ Male
☐ Female

Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)
Has this person ever been told by a healthcare professional that he/she has any of the following? Check all that apply:

- Epilepsy
- Seizures (not diagnosed as epilepsy)
- Migraine (severe headaches that can include nausea and vision problems)
- Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- Motor disability (problems with muscle movements, muscle control or posture)
- Autism spectrum disorder (problems with social interaction and communication skills)
- Depression (feelings of sadness, anxiety, hopelessness or worry)
- Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- Bipolar disorder (severe mood swings, often between an excited and depressed state)
- ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- None of the above
- Don’t Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state “unknown”)

**If “Epilepsy” OR “Seizures, not diagnosed as epilepsy)” is indicated:**
How old was this person when he/she started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

- Staring seizures
- Convulsive seizures (jerking seizures)
- Febrile seizures (seizures with fever)
- Don’t Know

Has this person ever taken medication to treat his/her seizures?

- Yes
- No
- Don’t Know

(All participants in this section continue)

How many children does this person have?

- 0
- 1
- 2
- 3
- 4
- 5
- More than 5

**If any response except “0” is indicated:**
Have any of this person's children or grandchildren been told by a healthcare professional that they have any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don’t Know

Thank you. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants in this section continue)

**Repeat QUESTION BLOCK: FATHER’S SIBLINGS for UP TO FIVE SIBLINGS**

**If “More than 5” full or half brothers and sisters is indicated:**
We apologize but there is not enough space provided to enter health information for your child's father's additional siblings. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants in this section continue)

Please answer the following questions about your child's FATHER'S PARENTS (paternal grandparents).

Please answer the following questions about your child's FATHER'S FATHER (paternal grandfather).

Is this person still living?

☐ Yes
☐ No
Has this person ever been told by a healthcare professional that he has any of the following? Check all that apply:

- □ Epilepsy
- □ Seizures (not diagnosed as epilepsy)
- □ Migraine (severe headaches that can include nausea and vision problems)
- □ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- □ Motor disability (problems with muscle movements, muscle control or posture)
- □ Autism spectrum disorder (problems with social interaction and communication skills)
- □ Depression (feelings of sadness, anxiety, hopelessness or worry)
- □ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- □ Bipolar disorder (severe mood swings, often between an excited and depressed state)
- □ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- □ None of the above
- □ Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when he started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

- □ Staring seizures
- □ Convulsive seizures (jerking seizures)
- □ Febrile seizures (seizures with fever)
- □ Don't Know

Has this person ever taken medication to treat his seizures?

- □ Yes
- □ No
- □ Don’t Know

(All participants in this section continue)

Please answer the following questions about your child's FATHER'S MOTHER (paternal grandmother).

Is this person still living?

- □ Yes
- □ No
Has this person ever been told by a healthcare professional that she has any of the following? Check all that apply:

- Epilepsy
- Seizures (not diagnosed as epilepsy)
- Migraine (severe headaches that can include nausea and vision problems)
- Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- Motor disability (problems with muscle movements, muscle control or posture)
- Autism spectrum disorder (problems with social interaction and communication skills)
- Depression (feelings of sadness, anxiety, hopelessness or worry)
- Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- Bipolar disorder (severe mood swings, often between an excited and depressed state)
- ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- None of the above
- Don't Know

**If “Epilepsy” is indicated:
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:
How old was this person when she started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

- Staring seizures
- Convulsive seizures (jerking seizures)
- Febrile seizures (seizures with fever)
- Don't Know

Has this person ever taken medication to treat her seizures?

- Yes
- No
- Don't Know

(All participants continue)

Please answer the following questions about your child's MOTHER'S SISTERS AND BROTHERS (maternal aunts and uncles).

**If “No” is indicated to “Are you able to answer questions about the child’s mother’s family members...”:
You have indicated that you do not have information about your child’s mother’s family. Please continue to the next page.

(All participants in this section continue)
How many full or half brothers and sisters does your child's mother have?

☐ 0
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ More than 5

**If "0" is indicated:**
You have indicated that your child's mother has no full or half siblings. Please continue to the next page.

**QUESTION BLOCK: MOTHER'S SIBLINGS**

**If any response except "0" full or half brothers and sisters is indicated:**
Please answer the following questions about your child’s MOTHER’S FIRST SIBLING.

For the mother's first sibling, is he/she a full sibling or half sibling to the mother?

☐ Full sibling
☐ Half sibling through the his mother
☐ Half sibling through his mother

Is this person still living?

☐ Yes
☐ No

What is this person's sex?

☐ Male
☐ Female

Is this person a twin?

☐ No
☐ Yes - Identical (Same)
☐ Yes - Not Identical (Fraternal)

Has this person ever been told by a healthcare professional that he/she has any of the following? Check all that apply:

☐ Epilepsy
☐ Seizures (not diagnosed as epilepsy)
☐ Migraine (severe headaches that can include nausea and vision problems)
☐ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
☐ Motor disability (problems with muscle movements, muscle control or posture)
☐ Autism spectrum disorder (problems with social interaction and communication skills)
☐ Depression (feelings of sadness, anxiety, hopelessness or worry)
☐ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
☐ Bipolar disorder (severe mood swings, often between an excited and depressed state)
☐ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
☐ None of the above
☐ Don't Know
**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren’t sure, please state “unknown”)

**If “Epilepsy” OR “Seizures, not diagnosed as epilepsy)” is indicated:**
How old was this person when he/she started having seizures?
(Drop Down Menu)

What type(s) of seizures does/did this person have? Check all that apply:

- □ Staring seizures
- □ Convulsive seizures (jerking seizures)
- □ Febrile seizures (seizures with fever)
- □ Don’t Know

Has this person ever taken medication to treat his/her seizures?

- □ Yes
- □ No
- □ Don’t Know

(All participants in this section continue)

How many children does this person have?

- □ 0
- □ 1
- □ 2
- □ 3
- □ 4
- □ 5
- □ More than 5

**If any response except “0” is indicated:**
Have any of this person’s children or grandchildren been told by a healthcare professional that they have any of the following? Check all that apply:

- □ Epilepsy
- □ Seizures (not diagnosed as epilepsy)
- □ Migraine (severe headaches that can include nausea and vision problems)
- □ Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- □ Motor disability (problems with muscle movements, muscle control or posture)
- □ Autism spectrum disorder (problems with social interaction and communication skills)
- □ Depression (feelings of sadness, anxiety, hopelessness or worry)
- □ Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- □ Bipolar disorder (severe mood swings, often between an excited and depressed state)
- □ ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- □ None of the above
- □ Don’t Know
Thank you. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants in this section continue)

**Repeat QUESTION BLOCK: MOTHER’S SIBLINGS for UP TO FIVE SIBLINGS**

**If “More than 5” full or half brothers and sisters is indicated:**
We apologize but there is not enough space provided to enter health information for your child’s mother’s additional siblings. The researcher will ask you about these persons during your follow-up telephone interview.

(All participants in this section continue)

Please answer the following questions about your child's MOTHER'S PARENTS (maternal grandparents).

Please answer the following questions about your child's MOTHER’S FATHER (maternal grandfather).

Is this person still living?
- [ ] Yes
- [ ] No

Has this person ever been told by a healthcare professional that he has any of the following? Check all that apply:
- [ ] Epilepsy
- [ ] Seizures (not diagnosed as epilepsy)
- [ ] Migraine (severe headaches that can include nausea and vision problems)
- [ ] Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- [ ] Motor disability (problems with muscle movements, muscle control or posture)
- [ ] Autism spectrum disorder (problems with social interaction and communication skills)
- [ ] Depression (feelings of sadness, anxiety, hopelessness or worry)
- [ ] Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- [ ] Bipolar disorder (severe mood swings, often between an excited and depressed state)
- [ ] ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- [ ] None of the above
- [ ] Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren’t sure, please state “unknown”)

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when he started having seizures?
(Drop Down Menu)
What type(s) of seizures does/did this person have? Check all that apply:

- Staring seizures
- Convulsive seizures (jerking seizures)
- Febrile seizures (seizures with fever)
- Don't Know

Has this person ever taken medication to treat his seizures?

- Yes
- No
- Don't Know

(All participants in this section continue)

Please answer the following questions about your child's MOTHER'S MOTHER (maternal grandmother).

Is this person still living?

- Yes
- No

Has this person ever been told by a healthcare professional that she has any of the following? Check all that apply:

- Epilepsy
- Seizures (not diagnosed as epilepsy)
- Migraine (severe headaches that can include nausea and vision problems)
- Cognitive disability (problems with learning, language or social skills, including developmental delays and learning delays)
- Motor disability (problems with muscle movements, muscle control or posture)
- Autism spectrum disorder (problems with social interaction and communication skills)
- Depression (feelings of sadness, anxiety, hopelessness or worry)
- Anxiety disorder (feelings of worry, uneasiness and fear of uncertain events)
- Bipolar disorder (severe mood swings, often between an excited and depressed state)
- ADD/ADHD (problems with attention, hyperactivity or impulsiveness)
- None of the above
- Don't Know

**If “Epilepsy” is indicated:**
What specific epilepsy syndrome was this person diagnosed with?

(If no specific diagnosis was given or if you aren't sure, please state "unknown")

**If “Epilepsy” OR “Seizures (not diagnosed as epilepsy)” is indicated:**
How old was this person when she started having seizures?

(Drop Down Menu)
What type(s) of seizures does/did this person have? Check all that apply:

☐ Staring seizures
☐ Convulsive seizures (jerking seizures)
☐ Febrile seizures (seizures with fever)
☐ Don't Know

Has this person ever taken medication to treat her seizures?

☐ Yes
☐ No
☐ Don't Know

Please answer the following questions concerning your availability to schedule a follow-up phone call with the researcher.

When is the best time to reach you during the day? Check all that apply:

☐ Morning
☐ Afternoon
☐ Evening

What is the best phone number to reach you?

____________________________

Thank you for participating in this survey! Your answers are very important to us.

A researcher will be contacting you shortly to schedule a follow-up phone call.

____________________________

*Double lines indicate the start of a new section = New page in online survey
** Indicates where skip logic is present. Instructions in bold.
### Appendix B: Data Abstraction Form

<table>
<thead>
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<th>Heading</th>
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<th>Response Options</th>
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<th>Variable Name</th>
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# Seizure Types

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<tr>
<td>Complex partial</td>
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<td>Epileptic Spasm</td>
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<td>Generalized Tonic-clonic</td>
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<td>Simple partial</td>
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<td>Tonic</td>
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<td>Tonic-Clonic</td>
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<td>Myoclonic</td>
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<td>Generalized-atypical absence</td>
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<td>Gelastic</td>
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<tr>
<td>Other</td>
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</table>

# Seizure Count

- Atonic: 1
- Complex partial: 2
- Epileptic Spasm: 3
- Generalized Tonic-clonic: 4
- Simple partial: 5
- Tonic: 6
- Tonic-Clonic: 7
- Myoclonic: 8
- Generalized-atypical absence: 9
- Gelastic: 10
- Other: 11

# MRI Imaging Normality

- Normal: 0 = Non Lesional
- Abnormal Unrelated: 1 = Lesional
- Abnormal both related and unrelated: 1 = Lesional
- Abnormal related: 1 = Lesional
- Abnormal unrelated: 1 = Lesional
- Abnormal possibly related: 1 = Lesional

# Phase 2

- # of Grids placed: [number]
  - 0 = No grid placement
  - 1 = grid placement

# Therapeutic Intervention

- Antiepileptic Tx: [list of medications]
  - # = total number of unique medications
- Past Antiepileptic Tx: [list of medications]
**Surgery**

**Repeat for all surgeries**

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<thead>
<tr>
<th>Type</th>
<th>Anterior Temporal Lobectomy</th>
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<td>Test (post-surgery)</td>
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<td>Tuber - documented TS</td>
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Appendix C: Response Rate Flowchart

156 individuals were contacted
Identified via CEC Database

52 individuals completed the
questionnaire
(35.1% response rate)

8 individuals were excluded

1 individual was lost to follow-up regarding ILAE outcome data and proband comorbidities
Appendix D: Expanded Demographics

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<tr>
<th>Expanded Participant Demographics</th>
<th>ILAE = 1 n (%)</th>
<th>ILAE &gt; 1 n (%)</th>
<th>Total n (%)</th>
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<td>26-35</td>
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<td>36-45</td>
<td>11 (45.8)</td>
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<td>7 (25.9)</td>
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<td>56-60</td>
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<td>9 (17.3)</td>
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<td>Two year college or technical school degree</td>
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<td>1 (1.9)</td>
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<td>Employed, part-time</td>
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<td>5 (18.5)</td>
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<td>2 (3.8)</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>Age Ranges, current age (years)</td>
<td>ILAE = 1 n (%)</td>
<td>ILAE &gt; 1 n (%)</td>
<td>Total n (%)</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>----------------</td>
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</tr>
<tr>
<td>0 - 5</td>
<td>2 (8.3)</td>
<td>2 (7.4)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>6 - 11</td>
<td>8 (33.3)</td>
<td>7 (25.9)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>12 - 17</td>
<td>7 (29.2)</td>
<td>11 (40.7)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>18 - 24</td>
<td>7 (29.2)</td>
<td>7 (25.9)</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td><strong>Mean current age</strong></td>
<td><strong>13.1 years</strong></td>
<td><strong>13.5 years</strong></td>
<td><strong>13.4 years</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Ranges, age at surgery (years)</th>
<th>ILAE = 1 n (%)</th>
<th>ILAE &gt; 1 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>10 (41.7)</td>
<td>8 (29.6)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>6 - 11</td>
<td>5 (20.8)</td>
<td>9 (33.3)</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>12 - 17</td>
<td>9 (37.5)</td>
<td>10 (37.0)</td>
<td>20 (38.5)</td>
</tr>
<tr>
<td><strong>Mean age at surgery</strong></td>
<td><strong>8.2 years</strong></td>
<td><strong>9.2 years</strong></td>
<td><strong>8.8 years</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Ranges, age at most recent evaluation (years)</th>
<th>ILAE = 1 n (%)</th>
<th>ILAE &gt; 1 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>3 (12.5)</td>
<td>3 (11.1)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>6 - 11</td>
<td>8 (33.3)</td>
<td>6 (22.2)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>12 - 17</td>
<td>9 (37.5)</td>
<td>13 (48.1)</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>18 - 24</td>
<td>4 (16.7)</td>
<td>5 (18.5)</td>
<td>9 (17.6)</td>
</tr>
<tr>
<td><strong>Mean age at most recent evaluation</strong></td>
<td><strong>11.7 years</strong></td>
<td><strong>13.0 years</strong></td>
<td><strong>12.4 years</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Ranges, from surgery to most recent evaluation (months)</th>
<th>ILAE = 1 n (%)</th>
<th>ILAE &gt; 1 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 18</td>
<td>1 (4.2)</td>
<td>3 (11.1)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>19 - 36</td>
<td>8 (33.3)</td>
<td>8 (29.6)</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>37 - 54</td>
<td>9 (37.5)</td>
<td>11 (40.7)</td>
<td>20 (39.2)</td>
</tr>
<tr>
<td>55 - 72</td>
<td>4 (16.7)</td>
<td>4 (14.8)</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>73 +</td>
<td>2 (8.3)</td>
<td>1 (3.7)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td><strong>Mean time from surgery to most recent evaluation</strong></td>
<td><strong>44.7 months</strong></td>
<td><strong>41.0 months</strong></td>
<td><strong>42.7 months</strong></td>
</tr>
</tbody>
</table>

ILAE outcomes are based on most recent clinical evaluation
For ILAE = 1, n = 24; For ILAE > 1, n = 27; Total n = 52
Abbreviations: ILAE = International League Against Epilepsy
Appendix E: Expanded Table 3

Mean proportion of affected relatives v. general population rates for individual comorbidities

<table>
<thead>
<tr>
<th>Measure</th>
<th>Proportion of affected FDRs Mean</th>
<th>SD</th>
<th>p-value</th>
<th>Proportion of affected SDRs Mean</th>
<th>SD</th>
<th>p-value</th>
<th>Proportion of affected TDRs Mean</th>
<th>SD</th>
<th>p-value</th>
<th>Proportion of affected total relatives Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>0.112</td>
<td>0.129</td>
<td>&lt;0.001</td>
<td>0.027</td>
<td>0.055</td>
<td>0.090</td>
<td>0.044</td>
<td>0.096</td>
<td>0.772</td>
<td>0.049</td>
<td>0.053</td>
<td>0.215</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.104</td>
<td>0.180</td>
<td>0.878</td>
<td>0.086</td>
<td>0.139</td>
<td>0.485</td>
<td>0.035</td>
<td>0.093</td>
<td>&lt;0.001</td>
<td>0.072</td>
<td>0.104</td>
<td>0.057</td>
</tr>
<tr>
<td>Autism</td>
<td>0.046</td>
<td>0.106</td>
<td>0.020</td>
<td>0.000</td>
<td>0.000</td>
<td>.</td>
<td>0.020</td>
<td>0.061</td>
<td>0.281</td>
<td>0.018</td>
<td>0.029</td>
<td>0.091</td>
</tr>
<tr>
<td>Bipolar</td>
<td>0.029</td>
<td>0.085</td>
<td>0.226</td>
<td>0.044</td>
<td>0.093</td>
<td>0.028</td>
<td>0.014</td>
<td>0.044</td>
<td>0.884</td>
<td>0.032</td>
<td>0.061</td>
<td>0.054</td>
</tr>
<tr>
<td>Cognitive Disability</td>
<td>0.207</td>
<td>0.135</td>
<td>0.843</td>
<td>0.019</td>
<td>0.061</td>
<td>&lt;0.001</td>
<td>0.019</td>
<td>0.061</td>
<td>&lt;0.001</td>
<td>0.059</td>
<td>0.045</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>0.170</td>
<td>0.239</td>
<td>0.001</td>
<td>0.140</td>
<td>0.171</td>
<td>0.001</td>
<td>0.036</td>
<td>0.088</td>
<td>0.157</td>
<td>0.106</td>
<td>0.128</td>
<td>0.005</td>
</tr>
<tr>
<td>Motor Disability</td>
<td>0.096</td>
<td>0.127</td>
<td>&lt;0.001</td>
<td>0.015</td>
<td>0.043</td>
<td>0.108</td>
<td>0.003</td>
<td>0.017</td>
<td>0.498</td>
<td>0.028</td>
<td>0.038</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.157</td>
<td>0.221</td>
<td>0.771</td>
<td>0.060</td>
<td>0.116</td>
<td>&lt;0.001</td>
<td>0.020</td>
<td>0.050</td>
<td>&lt;0.001</td>
<td>0.064</td>
<td>0.083</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epilepsy/Seizures</td>
<td>0.032</td>
<td>0.091</td>
<td>0.085</td>
<td>0.027</td>
<td>0.064</td>
<td>0.062</td>
<td>0.025</td>
<td>0.105</td>
<td>0.322</td>
<td>0.026</td>
<td>0.049</td>
<td>0.026</td>
</tr>
</tbody>
</table>

p Values from Fisher’s exact test; n = 52

Abbreviation: FDRs = first degree relatives; SDRs = second degree relatives; TDRs = third degree relatives; ADHD = attention deficit hyperactivity disorder; SD = standard deviation
Appendix F

Percentage of affected probands (self-reported data) v. ILAE outcomes at 1 year follow-up

<table>
<thead>
<tr>
<th>Measure</th>
<th>n Affected (%)</th>
<th>Aff: ILAE = 1</th>
<th>Aff: ILAE &gt; 1</th>
<th>Unaff: ILAE = 1</th>
<th>Unaff: ILAE &gt;1</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC (bin)</td>
<td>18 (40.9)</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>13</td>
<td>0.767</td>
</tr>
<tr>
<td>OTH (bin)</td>
<td>38 (86.3)</td>
<td>16</td>
<td>22</td>
<td>5</td>
<td>1</td>
<td>0.088</td>
</tr>
<tr>
<td>ANY (bin)</td>
<td>40 (90.9)</td>
<td>17</td>
<td>23</td>
<td>4</td>
<td>0</td>
<td>0.044</td>
</tr>
<tr>
<td>ADHD</td>
<td>13 (29.5)</td>
<td>4</td>
<td>9</td>
<td>17</td>
<td>14</td>
<td>0.194</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10 (22.7)</td>
<td>5</td>
<td>5</td>
<td>16</td>
<td>18</td>
<td>1.000</td>
</tr>
<tr>
<td>Autism</td>
<td>8 (18.2)</td>
<td>3</td>
<td>5</td>
<td>18</td>
<td>18</td>
<td>0.701</td>
</tr>
<tr>
<td>Bipolar</td>
<td>3 (6.82)</td>
<td>1</td>
<td>2</td>
<td>20</td>
<td>21</td>
<td>1.000</td>
</tr>
<tr>
<td>Cognitive Disability</td>
<td>35 (79.5)</td>
<td>16</td>
<td>19</td>
<td>5</td>
<td>4</td>
<td>0.716</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (22.7)</td>
<td>5</td>
<td>5</td>
<td>16</td>
<td>18</td>
<td>1.000</td>
</tr>
<tr>
<td>Motor Disability</td>
<td>19 (43.2)</td>
<td>10</td>
<td>9</td>
<td>11</td>
<td>14</td>
<td>0.761</td>
</tr>
<tr>
<td>Migraine</td>
<td>8 (18.2)</td>
<td>5</td>
<td>3</td>
<td>16</td>
<td>20</td>
<td>0.449</td>
</tr>
</tbody>
</table>

p Values from Fisher’s exact test; n = 44
Percentages calculated by multiplying the proportion of affected probands by 100
ILAE outcomes are based on clinical evaluation at one year post-surgery
Abbreviation: ILAE = International League Against Epilepsy; Aff = affected; Unaff = Unaffected; PSC = Psychiatric comorbidities (ADHD, anxiety, bipolar disorder, depression); OTH = Other neurologic comorbidities (autism, cognitive disability, motor disability, migraine); ANY (bin) = any comorbidities (ADHD, anxiety, autism, bipolar disorder, cognitive disability, depression, epilepsy/seizures, motor disability, migraine); ADHD = attention deficit hyperactivity disorder; SD = standard deviation
Appendix G

Percentage of probands diagnosed pre-surgery v. ILAE outcomes at most recent follow-up

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total n</th>
<th>n Affected (%)</th>
<th>ILAE = 1</th>
<th>ILAE &gt; 1</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>48</td>
<td>10 (20.8)</td>
<td>2 (9.1)</td>
<td>8 (30.8)</td>
<td>0.085</td>
</tr>
<tr>
<td>Anxiety</td>
<td>43</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
<td>0.488</td>
</tr>
<tr>
<td>Autism</td>
<td>50</td>
<td>7 (14.0)</td>
<td>0 (0)</td>
<td>7 (26.9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Bipolar</td>
<td>51</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cognitive disability</td>
<td>46</td>
<td>33 (71.7)</td>
<td>10 (47.6)</td>
<td>23 (92.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>44</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Motor disability</td>
<td>46</td>
<td>14 (30.4)</td>
<td>8 (38.1)</td>
<td>6 (24.0)</td>
<td>0.349</td>
</tr>
<tr>
<td>Migraine</td>
<td>47</td>
<td>3 (6.4)</td>
<td>1 (4.5)</td>
<td>2 (8.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

p Values from Fisher’s exact test
Percentages calculated by multiplying the proportion of affected probands by 100
ILAE outcomes are based on clinical evaluation at most recent follow-up
Total n for each comorbidity is based on the number of individuals for which the reported comorbidity could be verified using medical records
Abbreviation: ILAE = International League Against Epilepsy; ADHD = attention deficit hyperactivity disorder; SD = standard deviation
Appendix H

Percentage of probands diagnosed pre-surgery v. ILAE outcomes at one year post-surgery

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>n Affected (%)</th>
<th>Aff: ILAE = 1</th>
<th>Aff: ILAE &gt; 1</th>
<th>Unaff: ILAE = 1</th>
<th>Unaff: ILAE &gt;1</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>42</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>17</td>
<td>17</td>
<td>0.698</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>19</td>
<td>1.000</td>
</tr>
<tr>
<td>Autism</td>
<td>43</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>18</td>
<td>19</td>
<td>1.000</td>
</tr>
<tr>
<td>Bipolar</td>
<td>44</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>21</td>
<td>22</td>
<td>1.000</td>
</tr>
<tr>
<td>Cognitive Disability</td>
<td>41</td>
<td>30</td>
<td>13</td>
<td>17</td>
<td>7</td>
<td>4</td>
<td>0.306</td>
</tr>
<tr>
<td>Depression</td>
<td>38</td>
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<td>0</td>
<td>1</td>
<td>18</td>
<td>19</td>
<td>1.000</td>
</tr>
<tr>
<td>Motor Disability</td>
<td>40</td>
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<td>7</td>
<td>7</td>
<td>12</td>
<td>14</td>
<td>1.000</td>
</tr>
<tr>
<td>Migraine</td>
<td>42</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>18</td>
<td>21</td>
<td>1.000</td>
</tr>
</tbody>
</table>

P Values from Fisher’s exact test
Percentages calculated by multiplying the proportion of affected probands by 100
ILAE outcomes are based on clinical evaluation at most recent follow-up
Total n for each comorbidity is based on the number of individuals for which the reported comorbidity could be verified using medical records
Abbreviation: ILAE = International League Against Epilepsy; Aff = affected; Unaff = unaffected; ADHD = attention deficit hyperactivity disorder; SD = standard deviation