SOCIAL MATTERS

BEFORE AND AFTER EPILEPSY SURGERY IN CHILDREN

Brain Center
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OLGA BRAAMS

Social *matters* before and after epilepsy surgery in children

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Social *matters* before and after epilepsy surgery in children

Sociale aspecten voor en na epilepsiechirurgie bij kinderen

(met een samenvatting in het Nederlands)

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Chapter 1

Introduction

Epilepsy surgery in children

Epilepsy is a disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures.[1] It is the most common chronic neurological disorder in children; approximately 4–5 per 1,000 children have epilepsy.[2] In up to 30% of the patients, epileptic seizures are not sufficiently controlled by anti-epileptic drugs (AED's).[3,4] Epilepsy surgery is a treatment aiming to cure epilepsy in patients with drug-resistant focal epilepsy with an identifiable epileptic zone that does not involve eloquent cortex and is easily accessible to surgical resection.[5-7] Epilepsy surgery has developed in the past two decades, both in our own center and Europe-wide:[8,9] the number of surgeries per year increased significantly, the mean disease duration decreased and the use of imaging, source localization, and invasive monitoring expanded. Although more complex surgeries were performed, the rate of successful seizure outcome remained stable and high; more than 70% of the children were completely seizure free at 2 years after surgery. Over time, an increasing proportion of children became free of AED use.[8,9] The childhood epilepsy surgery population is extremely diverse in terms of etiology, age at epilepsy onset, location and size of epileptic focus, frequency and severity of the seizures, and age at surgery. In many children – particularly in the youngest age group – frequent and severe epileptic discharges contribute to cognitive and developmental problems, more than can be explained by the epileptogenic disorder alone. This disproportional developmental vulnerability is called epileptic encephalopathy.[10] Early surgical treatment in these most severely affected patients is crucial to optimize developmental outcomes.[11]

From the many possible structural causes of epilepsy in children who undergo epilepsy surgery, malformations of cortical development (MCD) are the most common (39%), followed by cerebral tumors (27%) and hippocampal sclerosis (15%). In 6%, no lesion can be identified using histopathological tissue examination.[12] In the time period between 1990 and 2014, the average age at surgery in children was 9 years (sd = 5) in European centers, with a mean seizure onset age of 4 years (sd = 4) and epilepsy duration of 5 years (sd = 4).[12] Epilepsy surgery is now recognized as the most effective treatment for carefully selected patients.[13]

The only recent randomized controlled clinical trial of epilepsy surgery in children convincingly demonstrated what was already known for decades among pediatric epileptologists: in well-selected candidates, surgery not only leads to significantly higher seizure-freedom rates after one year, compared to children who continue on medical treatment (77 versus 7% respectively), it also improves behavior and quality of life.[14]

Cognitive functioning after epilepsy surgery in children

Global cognitive functioning is not negatively affected by epilepsy surgery in children.[15] Rather, epilepsy surgery can be a basis for further development. For example, research from our own group demonstrated that children whose mental development had been retarded or deteriorated by epilepsy restarted development after disconnection of the affected hemisphere.[16] In other studies, we showed that positive change in IQ was associated with reduction of AEDs after successful epilepsy surgery,[17] but also with higher parental education.[18] Neuropsychological functioning in children before and after epilepsy surgery has been extensively researched and well documented.[19-21] Due to sophisticated diagnostic techniques for detecting lateralization and localization of specific cognitive functions in the epileptic brain, significant unexpected negative effects of epilepsy surgery on neuropsychological functioning in children are scarce, but subtle deficits have been described. In a lexical fluency task, for example, our group has shown that adolescents produced words that were – both before and after epilepsy surgery – qualitatively equal to those produced by healthy peers, but that the words were less in number.[22] Also, a delay in the development of language has been shown in children between five and 15 years after surgery in the language-dominant temporal lobe.[23] Furthermore, development of verbal memory is subtly delayed after epilepsy surgery that included the left temporal lobe and not after resections that spared the left temporal lobe.[24] Regardless the hemisphere of surgery, visual memory performance increased less than predicted on the basis of pre-surgical performance, as established in the same group of children as examined in the study of verbal memory.[25]

Social cognition

Social cognition is an umbrella term for the cognitive and emotional processes required to interpret the behavior and internal states of others and to respond in an appropriate manner.[26,27] Social cognition is necessary for general social functioning, like engaging in social interactions in a manner consistent with age-appropriate expectations.[28] Examples are: showing empathy, keeping a secret, reading body language, sharing, and helping. All these activities require an awareness and interpretation of other people's emotions, motives, desires, and feelings. Human social cognition is usually studied in terms of Theory of Mind (ToM), which can be described as the ability to think about other people's minds.[29] Choosing a gift based on the interests of the receiver and not on one's owns, is an example of ToM that typically develops between the ages of three to five years.[30] The capacity to derive from another person's facial expression how she or he is feeling

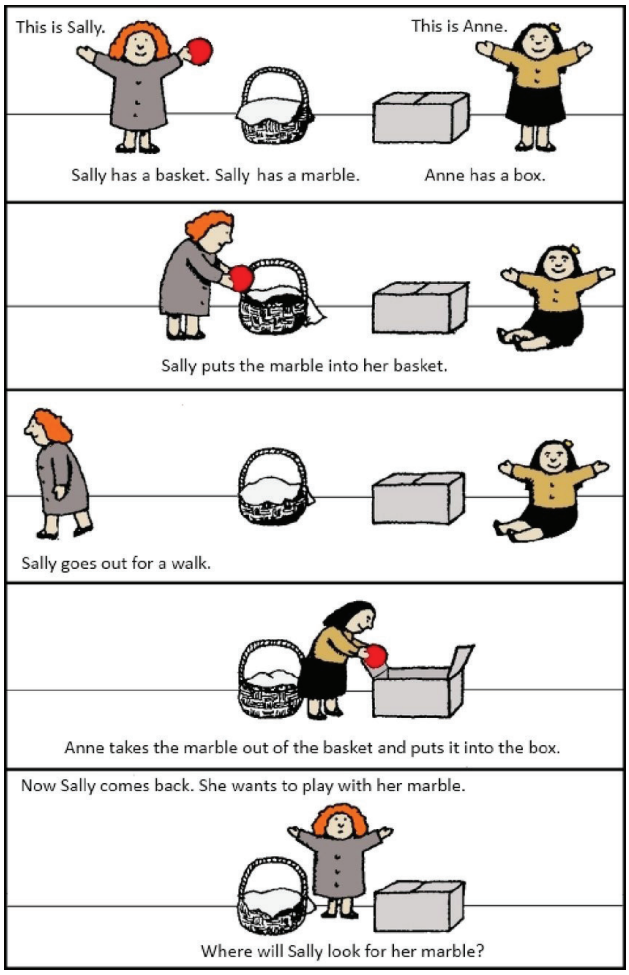


Figure 1.1: Illustration of the Sally & Anne task.
Source: Bolander 2014,[35] adapted from Frith 2001.[36]

is also considered an important component of ToM.[31] Two other components of ToM are understanding the difference between reality and thinking, dreaming and fantasizing and 'false belief', where the child has to be aware of the possibility that someone else can think something is true, while in reality it is different.[32] Figure 1.1 presents a famous example of a false belief task: the Sally and Anne task.[33,34]

Several neuroanatomical regions and networks are suggested to be involved in social cognition, at least in adults, including parts of the prefrontal cortex and superior temporal sulcus.[37] The amygdala in particular has been described as crucial in the cerebral mediation of social cognition.[38,39] Surgical treatments for refractory epilepsy often involve

Figure 1.2: Example items from the FEEST.[42]
The task consists of 36 (for children age < 12 years) or 60 (for children of 12 years of age or older) items. The faces were presented one by one to the children on a computer screen for three seconds each and express the six basic emotions: fear, disgust, sadness, anger, surprise, and happiness. The six textual emotion labels remained on the screen throughout the task. The child was asked to choose the emotion label that she or he thought the face expressed.

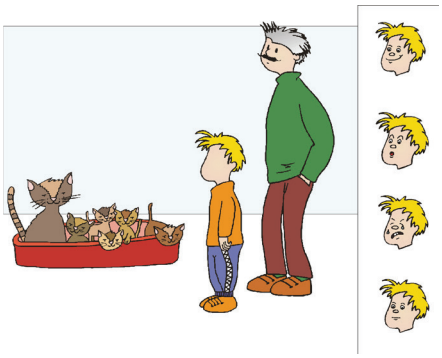
these structures.[13] Therefore, the expectation seems warranted that social cognition is influenced by epilepsy surgery, in addition to the negative influence that the epileptic disorder itself may have had on the development of the child's social cognition.

From a neuropsychological viewpoint, we were surprised to find that social cognition in children before and after epilepsy surgery had not been the topic of scientific research yet. From previous research by others we knew that ToM is at risk even in children with 'epilepsy only' and that this cannot be explained by lower intelligence.[40,41] Furthermore, a later onset of epilepsy is known to be associated with better ToM functioning, whereas AED-use does not relate to ToM functioning.[40,41] Effects of epilepsy surgery on ToM in children remained to be established and are a subject of the present thesis.

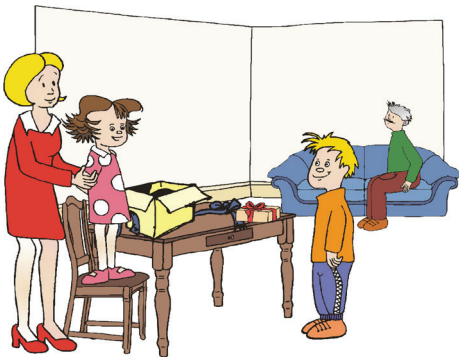
We used social cognition tasks. In the Facial Expression of Emotion: Stimuli and Tests (FEEST), emotions expressed by faces must be recognized (for examples see Figure 1.2).[42,43] The ToM Storybooks ('ToM-takenboek') (for examples see Figure 1.3) contains questions on different aspects of Theory of Mind that must be answered.[32] Furthermore, we selected questionnaires to assess personality of the children and probe parenting stress in their parents.

Social matters

Epileptic seizures are usually unpredictable and uncontrollable, which can render them dangerous and frightening, often requiring a continuously protecting environment. Having epilepsy has a large impact on quality of life (QoL) of the patient and the family.[44] Anxiety,[45] depression,[46] and fatigue[47] are common in parents of children with epilepsy and compromise parents' QoL.[48] Children with epilepsy face activity restrictions based



Sam is at his uncle who has kittens. Sam wants to take a kitten home. Daddy says they can't. How will Sam look?



It's Sam's birthday. His sister may look in the box. Sam can only touch the box. Who knows what is in the box?

Figure 1.3: Two example items from the ToM Storybooks.
Illustrated and provided by Els Blijd-Hoogewys. The ToM Storybooks are six books with various illustrated short stories with social storylines. The books are read to the child by an examiner who is sitting next to the child. The first example is from the book 'Sam on the farm'. The options for facial expressions are presented to the child through separate cards from which the child can choose one and then place it on the drawing of Sam. The second example is from the book 'Sam's birthday'.

on fear for risk of injury,[49] and their family's functioning suffers from restrictions imposed on family activities.[50] The stigma associated with having epilepsy, if present, negatively affects QoL and is strongly associated with seizure frequency.[51]

In children who are candidates for epilepsy surgery, the epilepsy is severe, refractory, and often long existing, causing an even larger effect on their own and their family's social wellbeing than in children with successful AED-treatment. Children with refractory epilepsy and their families have to adjust their lives to major restrictions and obligations. The better they adapt, the better they learn to live with the epilepsy. But what happens after epilepsy surgery? Surgery results in three possible new situations: i) not becoming seizure free and then having to adapt to an even more hopeless situation than before surgery, ii) becoming seizure free and having to adapt to a new, unknown situation, or iii) having seizure recurrence after a period of initial post-surgical seizure freedom, implying a loss of hope after having experienced the advantages of seizure freedom.

Very little is known about the social wellbeing of the parents after their child's epilepsy surgery. There is some evidence for improvement rather than normalization of QoL and emotional wellbeing in parents after (successful) epilepsy surgery of their child.[52]

Study population

Since the early nineties, pediatric epilepsy surgery in The Netherlands has been developed and exclusively performed in the University Medical Center Utrecht, yielding a unique opportunity to include a nation-wide and unselected epilepsy population in our research program. The work described in this thesis was part of a joint research project, performed in collaboration with Dr. J. Meekes, who investigated memory function before and after epilepsy surgery in children. For our project, we invited children who were candidates for epilepsy surgery between January 2008 and December 2010 to participate, by performing social cognition (and memory) tasks as an extension of their standard neuropsychological assessments before and 6, 12, and 24 months after surgery, and we asked parents to complete questionnaires. For every patient, two age- and sex-matched healthy control children were included.

Content of this thesis

The general aim of the research described in this thesis was to know whether social cognition was affected by epilepsy surgery in children. A broader context was provided by research on personality of these children and by research on psychological wellbeing of parents after their child's epilepsy surgery.

Part I, **Children** reports on social cognitive functioning and personality of children before and after epilepsy surgery. We compared data from patients before and after epilepsy surgery and compared their development with that of healthy peers. We exploratory searched for illness and demographic variables that could be associated with the results on the tasks or questionnaires. In **Chapter 2: Two years after epilepsy surgery in children: recognition of emotions expressed by faces** we analyzed results on the FEEST (Box 1.2). **Chapter 3: Epilepsy surgery no further threat for Theory of Mind in children** reports on ToM functioning using the ToM Storybooks (box 3). In **Chapter 4: Personality traits of children before and after epilepsy surgery** we present how children perceive themselves with respect to major personality traits by analyzing their completion of the Dutch Personality Questionnaire.

Part II, **Parents** reports on parenting stress and parents' psychological and family functioning. In **Chapter 5: Parenting stress does not normalize after child's epilepsy surgery** we used the Parenting Stress Index and we compared 1) results obtained before with those obtained two years after epilepsy surgery, and 2) responses from parents of surgically treated children with those from parents of healthy control children. For

Chapter 6: Parents experience problems in psychological and family functioning two to four years after their child's epilepsy surgery we approached a new cohort of parents of children who were operated after 2010; using the Brief Symptom Inventory we asked them to report on their own psychological functioning, and using the Family Questionnaire we inventoried their views with respect to their family functioning. We analyzed and studied the correlations between questionnaire results, child behavior, and illness and demographic variables.

Part III, **Overview** consists of two chapters. **Chapter 7: Social functioning in children after epilepsy surgery: a literature review** provides an overview of the existing research on social cognition and on general social functioning in children before and after epilepsy surgery. **Chapter 8 Summary and discussion** summarizes the conclusions of our research on social cognition, reflects on our methodological choices and provides suggestions for future research and clinical implications.

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Part I

Children

Chapter 2

Two years after epilepsy surgery in children: recognition of emotions expressed by faces

Olga Braams, Joost Meekes, Onno van Nieuwenhuizen, Renske Schappin, Peter van Rijen, Wencke Veenstra, Kees Braun, Aag Jennekens-Schinkel

Epilepsy Behav 2015;51:140-145

Abstract

Objectives: The purpose of this study was to determine whether children with epilepsy surgery in their history are able to recognize emotions expressed by faces and whether this recognition is associated with demographic variables [age, sex, and verbal intelligence (VIQ)] and/or epilepsy variables (epilepsy duration, side of the surgery, surgery area, resection of the amygdala, etiology, antiepileptic drug use, and seizure freedom).

Methods: Two years after epilepsy surgery, the Facial Expression of Emotion: Stimuli and Tests (FEEST) was administered to 41 patients (age: 4–20 years, mean: 13.5 years, 24 girls) and 82 age- and sex-matched healthy controls. Data obtained longitudinally (before surgery and 6, 12, and 24 months after surgery) in a small subset (11 patients and 22 matched controls) were explored to obtain clues about the course of REEF frombefore surgery.

Results: Corrected for VIQ, REEF scored significantly lower in the 41 surgically treated patients than in matched control children. No significant relationship was found between REEF and any epilepsy variable. Only age at assessment predicted REEF score in both patients and controls. The longitudinal data revealed a 'dip' in emotion recognition at the first postsurgical assessment in the six younger patients (age: < 12.1 years). The older patients (age: 13–17 years) showed a continuous increase in REEF scores that was similar to that in controls. Two years after surgery, REEF of the younger patients recovered to, but did not exceed, the presurgical level.

Conclusion: Neither poor REEF present two years after childhood epilepsy surgery, nor the aberrant course of REEF in younger patients (age: < 12.1 years) was explained by epilepsy variables or poor verbal intelligence. Disentangling the mechanism of the abnormality is urgently needed, as recognizing emotional expressions is a key component in the development of more complex social perception skills.

1. Introduction

Recognizing emotions expressed by faces (REEF) provides the perceiver information about another person's thoughts and feelings and is a key component in the development of more complex social perception skills.[1,2] Recognizing emotions expressed by faces appears to be at risk in both children and adultswith epilepsy.[3–6] However, consensus has not yet been reached with respect to the variables that are related to deficits in REEF. A lateralization effect has been suggested, but it has also been questioned.[6] The usually reported larger REEF deficit in adults with right-hemisphere epileptogenic foci than in those with left-hemisphere epileptogenic foci[4,5] has, for some emotions, been contradicted by the finding of lower REEF scores after left- than after right-sided surgery.[7] Localization of the epileptic foci may also play a role. In school-age children, a relationship was found between particular cerebral epileptogenic areas and specific facially expressed emotions. Whereas left and right temporal lobe epilepsies were associated with poor recognition of fear and disgust, respectively, frontocentral epilepsy was associated with poor recognition of happiness.[5] In the same study, Golouboff et al. found an association between early epilepsy onset and REEF deficits.[5] Associations between REEF and intelligence[6] or behavioral problems[5] have also been reported in patients with epilepsy.

Epilepsy surgery is increasingly performed in children, but the effect of epilepsy surgery on REEF in children is as yet unknown. In adults with temporal lobe epilepsy, the REEF deficit that was already present prior to epilepsy surgery did not change thereafter.[6]

In order to counsel parents and children appropriately, not only on epilepsy and cognition after surgery but also on the recognition of emotions, we studied REEF. We hypothesized that REEF is deficient in children after epilepsy surgery, and we explored associations of REEF with demographic variables (age at assessment, intelligence, and sex) and epilepsy variables (epilepsy duration, side of the surgery, surgery area, resection of the amygdala, etiology, antiepileptic drug use, and seizure freedom). We report on a controlled study of REEF two years after epilepsy surgery at a time when, presumably, the patients have adapted to their new life conditions. In addition, we tried to find a tentative answer to the question whether the deficit is incurred by the intervention or is already present before surgery. To this end, we report on the course of REEF from prior to epilepsy surgery up to two years after the surgery in the subset of patients and matched control children of whom longitudinal data were available.

2. Methods

The controlled study with consecutive inclusion of patients was part of a countrywide project addressing cognitive, affective, and psychosocial functioning of children and adolescents after epilepsy surgery.[8–10] The Institutional Review Board of the University Medical Center Utrecht approved the study. Parents of all children and also all children above the age of 12 years provided written informed consent.

2.1 Subjects

Two years after their epilepsy surgery, 41 children performed the test of recognizing facially expressed emotions (see Table 2.1 for demographic and epilepsy variables, as extracted from the medical records). For every patient, two age- and sex-matched control

Table 2.1: Demographic and epilepsy characteristics of patients (n = 41), assessed two years after epilepsy surgery

		Left/right
Sex (n)		
Girls	24	17 / 7
Boys	17	8 / 9
Age (years) at assessment [mean (sd)]	13.5 (4.4) (range: 4.2–20 y)	13.6 (4.0) / 13.4 (5.1)
Age (years) at epilepsy onset [mean (sd)]	5.9 (4.2)	5.9 (4.1) / 5.7 (4.6)
Duration of epilepsy (years) [mean (sd)]	5.6 (4.3)	5.6 (3.7) / 5.6 (5.1)
VIQ [mean (sd)]	84 (19.9)	85 (21) / 83 (18)
Etiology (n)		
Tumor	17[a]	11 / 6
MCD	12	8 / 4
Hippocampal sclerosis	5	2 / 3
Other	7[b]	4 / 3
Area and side of surgery (n)		
Temporal	17	12 / 5
Frontal	14	8 / 6
Central/parietal	8	4 / 4
Hemispherotomy	2	1 / 1
Amygdala (n)		
In situ	26	15 / 11
Resected	15	10 / 5

n = number; sd = standard deviation; VIQ = verbal intelligence quotient; MCD = malformation of cortical development.

[a] Ganglioglioma (n = 10), astrocytoma (n = 1), oligodendroglioma (n = 1), dysembryoplastic neuro-epithelial tumour (DNET) (n = 4); teratoma (n = 1).

[b] Tuberous sclerosis complex (TSC) (n = 2); traumatic brain injury (n = 1); DNET + dysplasia (n = 1); Rasmussen encephalitis (n = 1); cerebral infarction (n = 1); cavernoma (n = 1).

children without a neurological history were included. The 82 control children [mean age at assessment = 13.5 (sd = 4.4) years; 48 girls; mean VIQ = 112 (sd = 15.9)] were recruited from regular schools that were located in different neighborhoods with diverse socioeconomic backgrounds of a medium-sized nonuniversity town.

Longitudinal data on REEF were available for 11 of the 41 patients (see Table 2.2 for demographic and epilepsy data) [mean age at baseline = 11.9 (sd = 4.1) years; mean VIQ = 80 (sd = 14.0)] and for 22 matched healthy controls [mean age at last assessment = 11.9 (sd = 4.0) years; mean VIQ = 113 (sd = 15.1)]. Patients were assessed shortly before surgery (baseline) and 6, 12, and 24 months after surgery. The controls were assessed at similar intervals as their matching patient.

2.2 Instruments

2.2.1 Facial Expression of Emotion: Stimuli and Tests (FEEST)

The FEEST[11] assesses the recognition of facial expressions. The 60 black-and-white photographs of faces, taken from the 'Pictures of Facial Affect' series,[12] express the six so-called 'primary' or 'basic' emotions: happiness, anger, sadness, fear, surprise, and disgust. The faces were presented on a computer screen for 3 s each. The six textual emotion labels remained on the screen throughout the task. The child was asked to choose the emotion label that he thought the face expressed. The order of presentation of the faces was randomized. Validity of the FEEST is satisfactory.[11]

For children under the age of 12 years and/or children with lower cognitive abilities and/or a lower attention span, a shortened version was used (FEEST-36), consisting of a selection of 36 pictures from the original FEEST with six faces expressing the six emotions.[13] Upon presentation of each picture, the textual emotion labels on the screen were read out loud by the examiner.

In both versions of the FEEST, the proportion of correct responses was determined and analyzed. There were no structural differences between the two versions. In an ANOVA with proportions of correct responses as dependent variable and version, age, and the interaction between version and age as independent variables, the interaction was not significant: $F(1, 78) = 0.047$, $p = 0.83$, $\eta^2 < 0.01$; proportions of correct responses of controls did not differ between the versions when corrected for age.

2.2.2 Intelligence

Intelligence was assessed using a range of instruments, selected in conformity with the mandate of best clinical practice (e.g., Wechsler Intelligence Scale for Children-III [14,15]).

Table 2.2: Demographic and illness features of patients (n = 11), assessed before epilepsy surgery and 6, 12 and 24 months thereafter

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Sex	Boy	Boy	Boy	Boy	Girl	Girl	Girl	Girl	Girl	Girl	Girl
Age (years) at baseline	17.2	17.0	16.3	14.1	13.7	12.1	12.0	8.4	6.7	6.6	6.5
Age (years) at epilepsy onset	6	1	12	5	8	5	6	5	1	4	4
Epilepsy duration (years)	11	16	4	9	5	7	6	3	5	2	2
VIQ at baseline	97	81	77	67	74	83	69	69	73	82	110
Side of surgery	Right	Right	Right	Left	Left	Left	Left	Left	Left	Right	Left
Surgery area	Frontal	Temporal	Parietal	Temporal	Frontal	Temporal	Temporal	Frontal	Temporal	Frontal	Temporal
Amygdala	In situ	Resected	In situ	Resected	In situ	Resected	Resected	In situ	Resected	In situ	In situ
Etiology	Mature cystic teratoma	Ganglio-glioma	Ganglio-glioma	Protoplasmic astrocytoma	MCD	MTS	MCD	MCD	MTS	MCD	Ganglio-glioma

VIQ = verbal intelligence quotient; MCD = malformation of cortical development; MTS = mesial temporal sclerosis.

The verbal intelligence quotient (defined as 'VIQ') was used for analysis because labeling emotions is a predominantly verbal ability.

2.3 Data management and analyses

Statistical analyses were performed using IBM SPSS Statistics version 20.[16] In the large postsurgical study, differences between patients and controls (see Section 3.1.1) and influences on proportions of correct responses within both groups (see Sections 3.1.1 and 3.1.2) were examined with multivariate analysis of variance (MANOVA).

Proportions of correct responses to five of the six pictured emotions were used as outcome variables in the MANOVAs. Responses to pictures that represented 'happiness' were excluded from statistical analyses because of a near-ceiling effect (more than 90% of the 'happiness' responses were correct in both controls and patients), but descriptive statistics are reported where appropriate. When analyzing responses of controls and patients separately (see Sections 3.1.1 and 3.1.2), we studied influences of VIQ, age at assessment, and sex by including VIQ and age as covariates and sex as a factor in the MANOVA. Only VIQ was included as a covariate in the comparison of responses between controls and patients (see Section 3.2), since the control children were matched with the patients for age and sex.

Within the group of patients, we analyzed associations between the proportions of correct responses on each of the five emotions and epilepsy variables, including the duration of the epilepsy (years between epilepsy onset and surgery) as a covariate and the side of the surgery (left/right), surgery area (temporal, frontal, central/parietal, or hemispherotomy), surgical inclusion of the amygdala (yes/no), etiology [tumor, malformation of cortical development (MCD), hippocampal sclerosis, and other], antiepileptic drug use (two years after surgery, yes/no), and seizure freedom (no seizures during the two-year follow-up after surgery, yes/no) as factors in the MANOVA (see 3.2).

The two-year course of total proportions of correct responses was analyzed separately for patients and controls by means of linear mixed models (the advantage of linear mixed models over repeated measures analysis of variance being their capacity to handle small samples and unequal time intervals between measurements). The intercept was included as a random effect, with a scaled identity covariance structure. Because the sample size was small and there were only 4 time-points in the model, a random slope was not estimated, and the covariance structure of the repeated measures was scaled identity.

P-values < 0.05 were considered statistically significant, and p-values < 0.10 were reported as tendencies. Effect sizes (η^2) were considered small (> 0.01), moderate (> 0.06), or large

(> 0.14).[17] The use of multivariate statistical techniques, and, thus, a small number of analyses, rendered correction for multiple testing redundant.

3. Results

3.1 Two years after epilepsy surgery

3.1.1 Comparison of proportions of correct responses between controls and patients

Healthy control children had the highest proportions of correct responses on happiness (> 90% of the responses correct). The next highest average of correct responses pertained to surprise, followed by disgust, anger, sadness, and fear (Table 2.3, first column).

In the multivariate analysis, the proportions of correct responses of the control children were — both significantly and with a large effect size — associated with age: $F(5, 74) = 4.58$, $p < 0.01$, $\eta^2 = 0.24$; compared with younger children, older children chose more emotion labels correctly. Univariately, the relation with age was significant and had a moderate effect size for fear ($F = 11.23$, $p < 0.01$, $\eta^2 = 0.13$), surprise ($F = 6.46$, $p = 0.01$, $\eta^2 = 0.08$), and anger ($F = 6.51$, $p = 0.01$, $\eta^2 = 0.08$), whereas sadness was significantly related to age, but with a small effect size ($F = 5.28$, $p = 0.02$, $\eta^2 = 0.06$).

In the multivariate analysis, the proportions of correct responses of controls were not significantly related to VIQ ($F = 0.95$, $p = 0.45$, $\eta^2 = 0.06$) or sex ($F = 1.32$, $p = 0.27$, $\eta^2 = 0.08$).

Similar to the group of control children, the group of children who had been surgically treated labeled the facial expression of happiness almost perfectly. Their recognition

Table 2.3: Average proportions correct responses by controls and patients two years after epilepsy surgery, and comparison of group differences for each emotion category

	Proportion correct controls (n = 82) Mean (sd)	Proportion correct patients (n = 41) Mean (sd)	Difference between patients and controls	Univariate F(5, 116)	p	η^2
Happiness	0.99 (0.04)	0.97 (0.08)	0.02	NA	NA	NA
Anger	0.77 (0.17)	0.70 (0.22)	0.07	0.99	0.32	0.01
Fear	0.71 (0.26)	0.66 (0.24)	0.06	0.08	0.77	0.00
Surprise	0.82 (0.20)	0.63 (0.33)	0.19	4.67	**0.03**	0.04
Disgust	0.78 (0.23)	0.60 (0.30)	0.18	5.32	**0.02**	0.04
Sadness	0.77 (0.20)	0.58 (0.29)	0.19	5.73	**0.02**	0.05

sd = standard deviation.
Bold = statistically significant.

order of the other emotions differed somewhat from that in the control group: anger, fear, surprise, disgust, and sadness (in order of descending accuracy; Table 2.3, second column). As in controls, the multivariate analysis showed that proportions of correct responses of patients were, both significantly and with a large effect size, associated with age: $F(5, 33) = 5.62$, $p < 0.01$, $\eta^2 = 0.46$; older children chose more emotion labels correctly. Univariately, the association with age was significant for sadness ($F = 6.09$, $p = 0.02$, $\eta^2 = 0.14$) and surprise ($F = 27.55$, $p < 0.01$, $\eta^2 = 0.43$), both with large effects.

Multivariately, proportions of correct responses by patients tended to have a significant relationship with VIQ ($F = 2.34$, $p = 0.06$, $\eta^2 = 0.26$), with large effect size. The relation with sex was not significant ($F = 0.24$, $p = 0.94$, $\eta^2 = 0.04$). The tendency towards statistical significance in the presence of a large effect size suggests that the relation with VIQ exists but cannot be demonstrated because of the small group size.

Groupwise, surgically treated children had lower proportions of correct responses than matched healthy control children: multivariate $F(5, 116) = 2.31$, $p = 0.05$, $\eta^2 = 0.09$, a moderate effect size. Post hoc analyses revealed that the difference between patients and controls was significant for the proportions of correct responses of the emotion labels sadness, disgust, and surprise, albeit with small effect sizes (see Table 2.3). It should be noted that these differences were not explained by the difference in VIQ between patients and controls, as VIQ was controlled for in the analyses by including it as a covariate.

Because, in our longitudinal exploration (see Section 3.2), age appeared to influence the FEEST results of the younger patients (up to the age of 12.1 years at presurgical assessment), we divided these 41 patients and 82 controls into two subgroups with the age of 14.1 years (12.1 + the 2-year postsurgical follow-up) as the cutoff. Older patients had slightly (not significantly) lower proportions of correct responses. The pattern of their responses was almost similar to that in controls (see Figure 2.1a). In the younger children, not only the proportions of correct responses were lower, but also the pattern of responses deviated from that in controls. Again, differences between patients and controls were, corrected for VIQ, significant for sadness ($F = 4.18$, $p = 0.05$, $\eta^2 = 0.08$), disgust ($F = 5.84$, $p = 0.02$, $\eta^2 = 0.11$), and surprise ($F = 9.67$, $p < 0.01$, $\eta^2 = 0.17$), with moderate to large effect sizes (see Figure 2.1b).

3.1.2 Epilepsy variables associated with proportions of correct responses in patients

In the group of 41 patients, the multivariate analysis showed that none of the examined associations between epilepsy variables and proportions of correct responses were

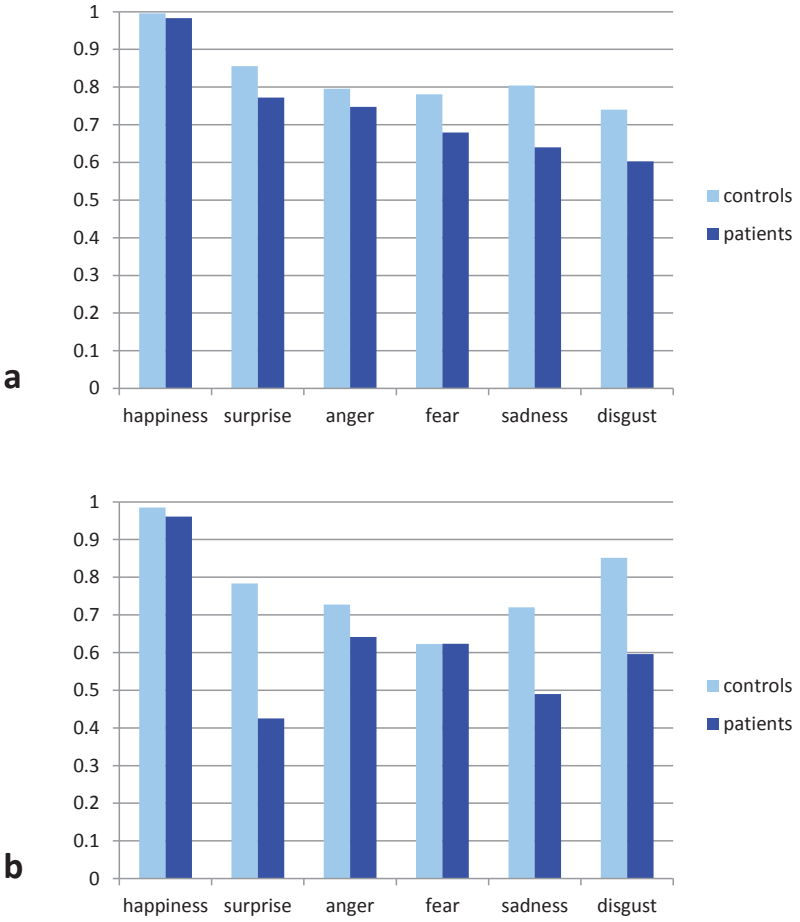

Figure 2.1: (a) Proportions of correct responses by controls (n = 47) and patients (n = 24) age > 14.1 years, shown for the six emotions. **(b)** Proportions of correct responses by controls (n = 35) and patients (n = 17) age ≤ 14.1 years, shown for the six emotions.

Table 2.4: MANOVA: associations between proportions of correct responses to the five emotions and epilepsy variables in patients (n = 41)

	F	df	p	η^2
Duration of epilepsy	1.353	5,25	0.31	0.20
Side of surgery	0.878	5,25	0.53	0.14
Surgery area	0.782	15,69	0.73	0.13
Amygdala resected/in situ	0.581	5,25	0.66	0.12
Etiology	0.770	15,69	0.79	0.12
Seizure freedom	0.985	5,25	0.45	0.17
AED use	0.212	5,25	0.95	0.04

significant (Table 2.4). Effect sizes were, however, large for duration of epilepsy, seizure freedom, and side of surgery. Directions of the relations between these variables and REEF were not consistent.

3.2 The course of proportions of correct responses: two-year follow-up with a presurgical baseline

Mean proportions of total correct responses in control children were 0.73 at the baseline, 0.77 at 6 months, 0.79 at 12 months, and 0.80 at 24 months thereafter (see Figure 2.2a). The increase over the four assessments was not solely due to the two-year increase of age: in the linear mixed model, the effect of age tended towards significance ($F = 0.25$, $p = 0.06$), whereas the effect of time for this two-year follow-up period was significant ($F = 9.60$, $p < 0.01$).

In the patients, mean proportions of total correct responses were 0.68 at baseline, 0.62 at 6 months, 0.68 at 12 months, and 0.69 at 24 months after epilepsy surgery (see Figure 2.2a), showing a 'dip' rather than an increase at the first postsurgical assessment. Two years after surgery, mean proportions of correct responses had recovered to, but barely beyond, the level prior to surgery (see Figure 2.2a).

Individual courses (Supplementary Figure S2.1) suggested an influence of age: the six patients who dipped at the first postsurgical assessment were the younger ones in the group. In those children (see Figure 2.2b), proportions of correct responses significantly differed between assessments ($F = 4.33$, $p = 0.02$). Post hoc analyses showed that the difference between baseline and first postsurgical assessment was significant (mean difference = -0.14, 95% CI = -0.23 to -0.05, $p = 0.05$). In these six younger patients, proportions of correct responses at baseline did not differ significantly from those 24 months after surgery (mean difference = -0.04, 95% CI = -0.01 to 0.05, $p = 0.34$). Older patients ($n = 5$, age > 12.1) showed no dip at the first postsurgical assessment (mean difference = 0.04; 95% CI = -0.02 to 0.11, $p = 0.14$), and over the two-year course (baseline compared to 24 months later), their proportions of correct responses increased significantly (mean difference = 0.07; 95% CI = 0.01 to 0.13, $p = 0.03$) (see Figure 2.2c). The 'dip' in younger patients was most prominent for recognizing surprise (-40%), followed by anger (-30%), disgust (-20%), and happiness (-7%). Recognizing fear and sadness did not decrease 6 months after epilepsy surgery.

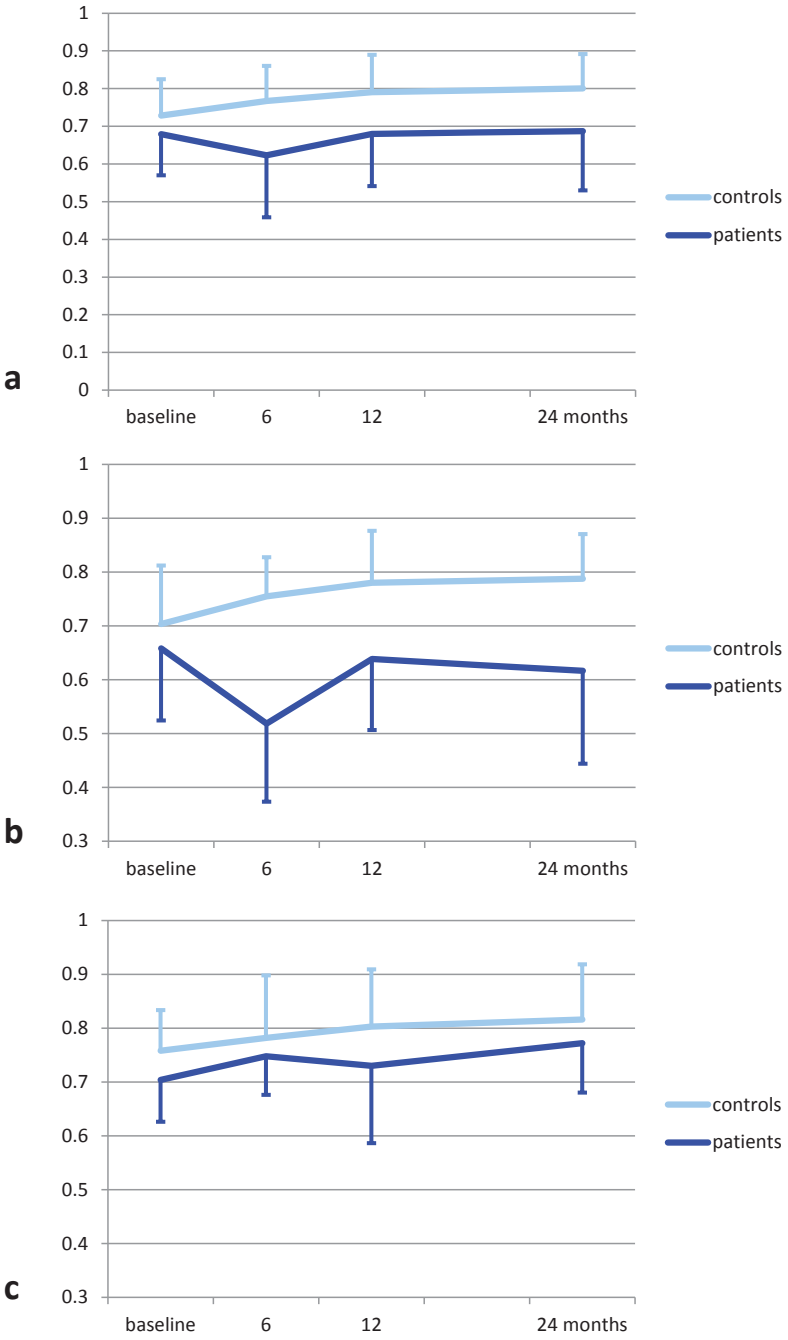

Figure 2.2: (a) Mean proportions of correct responses (whisker = sd) by controls (n = 22) and patients (n = 11), at baseline and 6, 12, and 24 months later. **(b)** Mean proportions of correct responses (whisker = sd) by younger (age ≤ 12.1 years) controls (n = 12) and patients (n = 6), at baseline and 6, 12 and 24 months later. **(c)** Mean proportions of correct responses (whisker = sd) by older (age > 12.1 years) controls (n = 10) and patients (n = 5), at baseline and 6, 12 and 24 months later.

4. Discussion

We found that, two years after epilepsy surgery, children had a deficit in recognizing emotions expressed by faces (REEF) when compared to age- and sex-matched controls. Patients recognized sadness, surprise, and disgust significantly less well than controls. For the present discussion, it is relevant that we retrospectively analyzed the results of two other tasks — memory for faces and memory for abstract line drawings (Test of Memory and Learning[9,18]) — using the same statistical model that was used to analyze the difference between patients and controls on the FEEST, controlling for VIQ. The absence of a significant difference on these two tasks ($F = 1.35$, $p = 0.26$, $\eta^2 = 0.03$) suggests that poor labeling of emotions by patients should not be attributed to e.g., a more general cognitive deficit.

As expected, age was a significant determinant, both in patients and in controls, with older children recognizing more emotions than younger children. Although none of the specific epilepsy variables were statistically significantly associated with REEF, effect sizes were large for the duration of the epilepsy (negative effect), seizure freedom (positive effect), and side of surgery (inconsistent effects per emotion).

From the small subset of children with longitudinal data, we learned that, whereas the older children increased REEF similar to controls, REEF of the younger children transiently decreased at the first postsurgical assessment and, in the majority, did not attain baseline over the following eighteen months. Given this difference, we divided the larger, postsurgical group with a similar age cutoff and found that the deficit in recognizing sadness, surprise, and disgust observed in the whole group could largely be attributed to the younger patients.

The notion of right hemisphere specialization for the expression and appreciation of emotions[19] is still prevalent. Accordingly, we expected that children with right-sided epilepsy would be at a disadvantage in REEF compared to children with left-sided epilepsy, c.q., resection. Although, in our study, lateralization of the surgery was not significantly related to REEF, the large effect sizes indicate that an association between the side of surgery and REEF is likely. When inspecting the effects for every emotion, we found a pattern (with poorer scores on fear in left-sided surgery patients and poorer scores on disgust in right-sided surgery patients) that might fit the previously suggested lateralization effect.[5] The effect should be further analyzed in a larger sample. In contrast to Golouboff et al.,[5] we found no significant influence of localization (as defined by cerebral lobe) of the epilepsy, neither of the site of resection. However, the studies are difficult to compare since Golouboff et al. did not include children younger than eight

years and used a different instrument with longer stimulus presentation and different statistical approaches.

Perhaps surprisingly, we found no relation between REEF and removal of the amygdala. In adults, the amygdala appears to be an important relay station of the emotion-processing network.[20,21] It is possible that the resected amygdala was already structurally or functionally affected before surgery, and hence, resection did not affect function. It is also conceivable that labeling pictured facial expressions of emotions is not specifically sensitive to functions of the amygdala. As Öhman suggested, the role of the amygdala may be particularly prominent in automatic, real-life emotional responses rather than in cognitive emotion labeling.[22] Last but not least, the role of the amygdala in REEF could be different in adults and children.

The postsurgical 'dip' and insufficient recovery of REEF in the younger patients suggest that REEF is more vulnerable to epilepsy surgery in younger children than in older children. However, alternative explanations cannot be excluded: the group of six younger children happened to consist of only girls, five of whom had surgery in the left cerebral hemisphere; and in the group of older children, tumors predominated (whereas, in the younger patients, MCD was the most frequent etiology).

The deficit in recognizing sadness, surprise, and disgust was significantly present in the group of younger patients, rather than in the older patients. Widen[23] suggests that labeling of emotions follows a developmental path starting with two broad valence-based categories, in which the label 'happy' stands for everything that 'feels good' and the label 'anger' stands for everything that 'feels bad'. Over time, children slowly use more and more specific labels when presented with different emotions (in the order anger, sadness, fear, disgust).[23] In this light, it might be proposed that, in our younger patients, the development of REEF is delayed rather than impaired: they scored relatively low on emotions that are differentiated later, and high on happiness (feels good). It may be surmised further that earlier developmental stages of REEF are more vulnerable to interventions such as epilepsy surgery.

We took care to control for possible influences of general cognitive functioning in order to specifically zoom in on REEF. Although VIQ was not significantly related to REEF, the large effect size indicates that children with a higher VIQ label pictures of facially expressed emotions better. The possibility that epilepsy surgery might be an additional — at least transient — risk factor in younger children should not be disregarded.

5. Limitations

The population of children who undergo epilepsy surgery is heterogeneous with regard to variables such as age, intelligence, etiology, and side and site of the surgery. Earlier research on REEF before and after epilepsy surgery in children has not been reported. While admitting that replication of our findings in larger and more homogeneous cohorts is necessary, we consider the inclusion of a large and well-matched control sample and the systematic follow-up assessments strengths of the study.

Rather than opting for a control group of children with a different chronic illness and/or a different (or no) surgical intervention, we included healthy children as a control group because the comparison with clinical groups would entail unwanted influences of illness-specific sets of variables. As the groups of patients and controls differed in intelligence, we controlled for this bias by including verbal intelligence in the analyses as a covariate.

The small size of the subgroup with longitudinal data did not allow further analysis of possible variables explaining the postsurgical dip of REEF in the younger patients.

We are aware that REEF depends not only on verbal IQ, but also on functions such as attention, language, perception, and memory.[24,25] Accounting for these associations was beyond our possibilities, the major reason being the disparate age limits of the tests, which limited the group sizes. Also, the retrospectively analyzed tasks were performed by only 36 out of the 41 patients. Notwithstanding these limitations, the relationship of VIQ with labeling emotions makes sense and offers clues for counseling and further research.

6. Conclusion

Recognition of emotions expressed by pictured faces is deficient in children two years after epilepsy surgery. This cannot be fully explained by lateralization of the epilepsy or by resection of the amygdala. Although verbal intelligence does not fully explain poor REEF either, the verbal loading of the task is reflected in the large effect size of VIQ. Recognizing emotions expressed by faces appears to be more vulnerable to epilepsy surgery in younger children than in older ones. However, none of the patients lost the ability to recognize any of the six emotions proportions of correct responses were only decreased. The presumably surgery-related deficit could be transitory, but our 24-month follow-up does not support this supposition. The present study requires replication in a larger group.

Highlights

- Recognizing emotions expressed by faces (REEF) is poor in children two years after epilepsy surgery.
- Sadness, surprise and disgust are less well recognized by patients than by healthy controls.
- Epilepsy variables do not significantly explain REEF deficits.
- REEF in young children (age < 12 years) is more vulnerable to epilepsy surgery than in older children.

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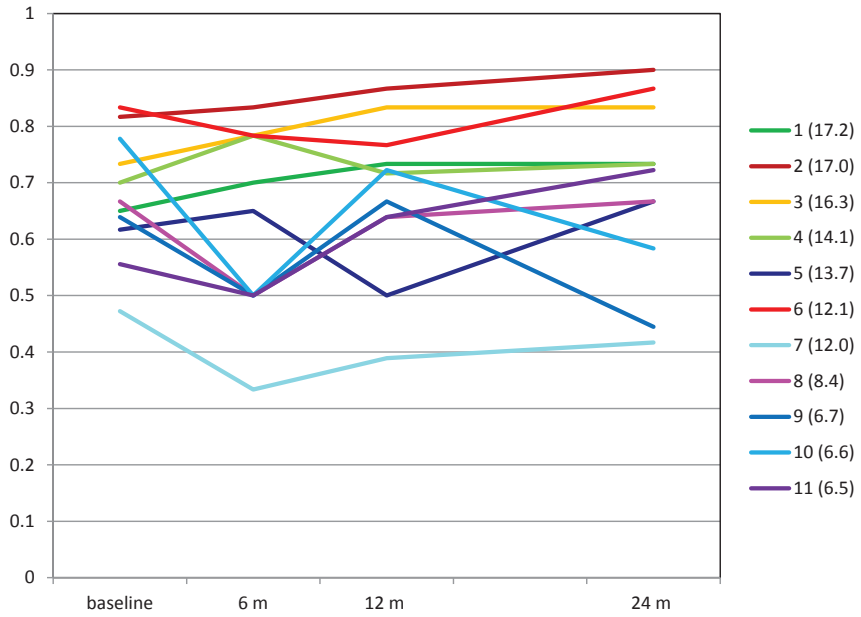
Supplementary data



Supplementary Figure S2.1: Proportions correct responses per individual patient [patient number (age)] prior to epilepsy surgery and 6, 12 and 24 months after epilepsy surgery.

Chapter 3

Epilepsy surgery no further threat for Theory of Mind in children

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Epileptic Disord. Accepted for publication

Abstract

Aims: To know whether Theory of Mind (ToM), an important requirement for adaptive social functioning, is different between children with pharmacologically refractory epilepsy who undergo epilepsy surgery and healthy control children, whether ToM is affected by epilepsy surgery in these children, and whether ToM is associated with demographic or epilepsy variables.

Methods: The 'ToM Storybooks', a psychometrically sound ToM instrument designed for children, was administered shortly before and 0.5, 1 and 2 years after surgery as part of a neuropsychological assessment. Fifteen patients (mean age 7.1 years) completed the ToM Storybooks before and at least twice after surgery. Two sex- and age-matched healthy control children were included per patient. Linear mixed models were used to analyze differences between patients and controls. In patients, relations between ToM with demographic and illness variables were explored.

Results: Patients had lower ToM scores than healthy control children, even when corrected for verbal intelligence quotient (VIQ). Epilepsy surgery had neither a harmful nor a favorable effect on ToM results. Later epilepsy onset and temporal origin of the epilepsy were associated with higher (better) ToM-scores than earlier epilepsy onset and than extra-temporal epilepsy (including hemispherotomy in one case). Children in whom the amygdala was resected performed worse on ToM.

Conclusion: Children with refractory epilepsy have a ToM deficit that is not explained by their lower VIQ. Epilepsy surgery does not affect ToM functioning. Younger age at epilepsy onset is associated with poorer ToM and temporal epilepsy with better ToM. Implication of the amygdala is related with worse ToM. Patients and their parents should be educated about the possible consequences of epilepsy for developing social cognition and guided to help improve ToM abilities.

1. Introduction

Theory of Mind (ToM) is an important ability for social functioning from early childhood on. Having ToM means that one is able to attribute 'mental states' such as feelings, intentions, beliefs and desires to others and to one-self. ToM allows one to predict behavior of others and to adapt one's own actions when interacting with others.[1,2] For example, when a nearly three-year-old child chooses a birthday gift for her father, she will probably pick a doll for him, not being able to differentiate between her own and her father's desires. The latter ability typically develops between the ages of 3 to 5 years.[3] A famous example of a ToM task is the 'Sally and Anne' test.[4,5] Sally and Anne are in a room. Sally has a basket and Anne has a box. Sally puts a marble in her basket and leaves the room, after which Anne takes the marble out of Sally's basket and puts it in her own box. Then Sally returns. The examiner asks the child where Sally will look for the marble. If the child lets Sally search in the place where she left the marble (rather than in the factual, new location), his/her answer reflects an awareness of the difference between factual and mental reality, an appreciation that Sally entertains a 'false belief'. Understanding the difference between reality and thinking, dreaming and fantasizing can, similarly, be conceived of as a ToM ability.[6]

Language comprehension is highly related to ToM functioning and can be considered an essential skill for developing ToM.[7,8]

ToM deficits have often been reported in adults with epilepsy, especially in patients with temporal lobe epilepsy.[9-11] Several neuroanatomical regions and networks have been suggested as being involved in ToM, including parts of the prefrontal cortex and superior temporal sulcus (for a review, see Carrington and Bailey, 2009).[12] The amygdala in particular has been described as crucial in the cerebral mediation of ToM.[13,14] However, surgery to treat temporal lobe epilepsy in adults appears to neither improve nor worsen ToM functioning.[15]

Despite its developmental significance for everyday functioning, research on ToM in pediatric epilepsy patients is scarce. ToM is at risk even in children with 'epilepsy only' and this cannot be explained by lower intelligence.[16,17] Furthermore, a later onset of epilepsy is associated with better ToM functioning, whereas anti-epileptic drug use is not related to ToM functioning.[16,17] Effects on ToM of surgical treatment of epilepsy surgery in children remain to be established. From a previous study, we did learn that epilepsy surgery causes a transient decrease in recognition of facially expressed emotions, one of the abilities that underlie ToM,[18] but only in children younger than 13 years at surgery at time of surgery.[19]

Given the importance of ToM for social functioning, the question whether epilepsy surgery affects the development of ToM over and beyond the deficit inflicted by the epilepsy per se is crucial for adequate pre-surgical counseling of parents and children. For the present paper we hypothesize that ToM is deficient in children with refractory epilepsy who are candidates for epilepsy surgery and that ToM does not change after epilepsy surgery. Taking that ToM is a more comprehensive ability than recognizing facial expressions, we expect ToM to be less prone to decline. To test our hypotheses, we explored associations of ToM with time (before surgery and 0.5, 1 and 2 years after surgery), demographic variables (age at assessment, intelligence and sex) and with epilepsy and surgical variables [epilepsy onset age, side and area of surgery, etiology, resection of the amygdala (by amygdalohippocampectomy), anti-epileptic drug use and post-surgical seizure status].

2. Methods

The controlled study with consecutive inclusion of patients was part of a countrywide project addressing cognitive, affective and psychosocial functioning of children and adolescents after epilepsy surgery.[19-21] The Institutional Review Board of the University Medical Center Utrecht approved the study. Parents of all children and also all children above the age of 12 years provided written informed consent.

2.1 Subjects

Between January 2008 and December 2010, 68 children underwent epilepsy surgery. Twenty-two of them were between four and 12 years of age at first assessment and met the age-criteria of the ToM instrument. Five of these children could not perform the ToM instrument due to poor cognitive functioning and/or severe behavioral problems, one child belonging to an ethnic minority group had insufficient command of the Dutch language, and one child underwent a second surgical intervention before completion of the follow-up. The 15 included patients performed the ToM instrument prior to surgery and at least two of the three post-surgical assessments (0.5, 1 and 2 years after surgery) (see Table 3.1 for demographic and epilepsy variables, as extracted from the medical records).

For every patient, two age- and sex-matched healthy control children were included. The 30 control children [mean age at assessment = 7.1 (sd = 2.3) years; 20 girls; mean VIQ = 110 (sd = 15.2)] were recruited in a medium-sized non-university town and a large university city, from regular schools with diverse socio-economic backgrounds.

Patients were assessed shortly before surgery (baseline) and 0.5, 1 and 2 years after the intervention. The controls were assessed at similar intervals.

Table 3.1: Demographic and epilepsy characteristics of patients (n = 15) at assessment before epilepsy surgery and seizure freedom thereafter

		Mean age years (sd)
Sex (n)		
Girls	10	7.3 (2.2)
Boys	5	6.9 (2.8)
Age at assessment		7.1 (2.3) (range 4.0–11)
Epilepsy onset		3.8 (2.6)
Duration of epilepsy		3.5 (1.7)
AED number (n)		
0	1	6.5 (---)
1	3	8.6 (3.2)
2	5	7.9 (2.4)
3	6	5.9 (1.4)
VIQ mean (sd)	80 (19.3)	
Side of surgery (n)		
Left	9	8.0 (1.8)
Right	6	5.9 (2.5)
Etiology (n)		
Cerebral tumor	5[a]	8.1 (2.6)
MCD	6	6.2 (1.8)
HS	2	5.4 (1.8)
Other	2[b]	9.2 (1.6)
Area of surgery (n)		
Temporal	6	7.2 (2.7)
Frontal	5	6.7 (1.7)
Central/parietal	3	7.5 (3.4)
Hemispherotomy	1	8.1 (---)
Amygdala (n)		
In situ	10	6.7 (2.1)
Resected	5	8.0 (2.7)
Seizure freedom*		
Yes	13	7.1 (2.1)
No	2	7.1 (4.5)

HS = hippocampal sclerosis; MCD = malformation of cortical development; n = number; sd = standard deviation; VIQ = verbal intelligence quotient.

[a] Ganglioglioma (n = 3), oligodendroglioma (n = 1), dysembryoplastic neuro-epithelial tumour (DNET) (n = 1).

[b] Cerebral infarction (n = 1); cavernoma (n = 1).

* Defined as complete seizure freedom from surgery until two years thereafter.

2.2 Instruments

2.2.1 Theory of Mind (ToM) Storybooks

The Theory-of-Mind Storybooks have been designed to assess ToM abilities in children between four and 12 years of age.[6] This instrument targets ToM development prior to the age of four and is applicable beyond that age. It has norm scores from the age of three up to 12 years and thus allows for comparisons between children of widely varying age, which renders the test particularly appropriate for use in clinical groups. The test consists of various illustrated short stories with social storylines. The drawings are colorful and enlivened with doors that open and separate response cards with faces expressing emotions that can be selected and placed on the characters. For an example see Appendix 3.1. In conformity with the instructions in the test manual, the six books are read to the child by an examiner who is sitting next to the child. 'How is Sam feeling?' is the first book, after which the child chooses the order of the following four books ('Sam goes to the park', 'Sam goes swimming', 'Sam visits his grandparents', 'Sam at the farm'). The sixth and final book is 'Sam's birthday'.

The tasks address different aspects of ToM, such as attributing emotion, desire and belief, and differentiating between reality and fantasy or dream. The result is expressed, as an overall ToM-score (ToM-Q). So-called 'test questions' refer to matters of fact (e.g., 'Where will Sam look for his rollerblades: in the toy trunk or in the box?'). For the 'justification questions', the child has to come up with a hypothesis about the story-character's mental state (e.g., 'Why will Sam look in the box?'). There are no time limitations for answering the questions. The results are converted to the so-called ToM-Q, an age-normed score with mean = 100 and standard deviation (sd) = 15. Higher scores indicate better ToM. Scores on the ToM Storybooks correlate strongly with intelligence and language skills.[6] The ToM Storybooks have satisfactory validity and good test-retest reliability, both for typically developing children and for children with Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS).[6,22]

2.2.2 Intelligence

Intelligence was assessed using a range of instruments, selected in conformity with the mandate of best clinical practice (e.g., Wechsler Intelligence Scale for Children-III).[23,24] The verbal intelligence quotient (VIQ) was used in the analyses to correct for differences between patients and control children because research has shown that ToM correlates strongly with verbal skills.[6,8]

2.3 Data management and analyses

Statistical analyses were performed using IBM SPSS Statistics version 20.[25] Differences between patients and controls (group) were examined using Linear Mixed Models (LMM), with age at assessment and VIQ as covariates, and group, time (pre- and 0.5, 1 and 2 years after surgery), and sex as factors. The advantage of LMM over repeated measures analysis of variance is their capacity to handle small samples and unequal time intervals between measurements (i.e., 0.5 year between the first two postoperative measurements and 1 year between assessments 3 and 4). The per-subject intercept and slope were included as random effects, with a scaled identity covariance structure for the intercept and an unstructured covariance structure for the slope.

Within the group of patients, we explored associations between ToM-Q and epilepsy variables, including the age at epilepsy onset, time (pre- and 0.5, 1 and 2 years after surgery) and number of anti-epileptic drugs used (reported at each assessment) as covariates. The side of epilepsy surgery (left/right), area of surgery [‘temporal only’/‘all other’ (frontal, central-parietal and hemispherotomy)], surgical inclusion of the amygdala (by amygdalohippocampectomy) (yes/no), etiology [tumor/malformation of cortical development (MCD)/hippocampal sclerosis /other)], and seizure freedom (no seizures during the two-years follow-up after surgery, yes/no) were included as factors in the LMM analysis. A further explorative LMM analysis was narrowed down to, besides time, those illness variables that exist from the first epileptic seizure, i.e., onset age, side and area of epilepsy focus (and of surgery), etiology and implication of the amygdala. VIQ was not included in these analyses, in order to prevent its relation with ToM-Q to conceal other possible relations. LMM analyses with VIQ rather than ToM-Q were performed in the same way, in order to clarify the degree to which VIQ and ToM-Q are predicted by the same variables (see Supplementary Tables S3.1 & S3.2). Due to the small size of the patient sample, interactions were not analyzed. P-values < 0.05 were considered statistically significant.

3. Results

3.1 Comparison of patients and control children with respect to ToM-Q and VIQ over time

Figure 3.1 shows scores for ToM-Q and VIQ of patients and control children over the two-years period.

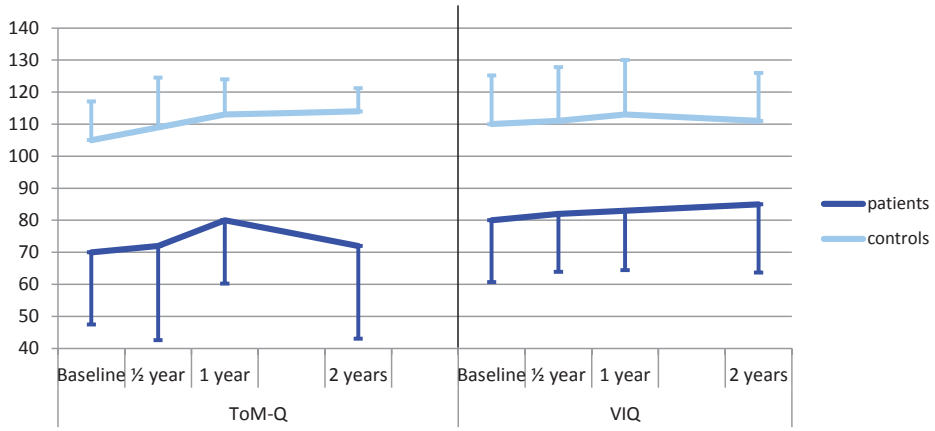

Figure 3.1: Two years follow-up scores of ToM-Q and VIQ for patients and healthy peers.

LMM analysis (Table 3.2) revealed that patients had a significantly lower average ToM-Q than healthy controls, when corrected for VIQ. [When not corrected for VIQ, the difference was also significant ($F = 32.4$, $p < .001$)].

VIQ was significantly positively related to ToM-Q. The significant interaction of group and age at assessment means that in control children ToM-Q was age-independent (what was to be expected since ToM-Q is age-normed), whereas in patients ToM-Q increased with age (Figure 3.2). There was no significant relation of ToM-Q with either (follow-up) time or sex.

Table 3.2: LMM analysis of ToM-Q: effects of group, sex, time and age, and interaction of group with age on ToM-Q (corrected for VIQ)

		95% CI				
	Estimate	Lower bound	Upper bound	F	df	p
Intercept	35.84	13.04	58.63	1.307	65.64	.257
Group[a]	-53.56	-74.53	-32.60	26.239	53.88	**< .001**
Sex[b]	3.07	-2.49	8.63	1.254	36.62	.270
Time*	0.11	-2.97	3.20	.005	57.12	.942
Age at assessment	5.55	3.65	7.45	30.102	41.57	**< .001**
Group x age at assessment[c]	4.25	1.89	6.61	13.052	55.94	**.001**
VIQ	0.55	0.40	0.70	55.175	75.56	**< .001**

CI = confidence interval.
[a] Statistics for patients; control group is reference.
[b] Statistics for girls; boy group is reference.
[c] Statistics for patients x age; control x age is reference.
* Time = presurgical and ½, 1 and 2 years post surgery.
Bold = $p < 0.05$.

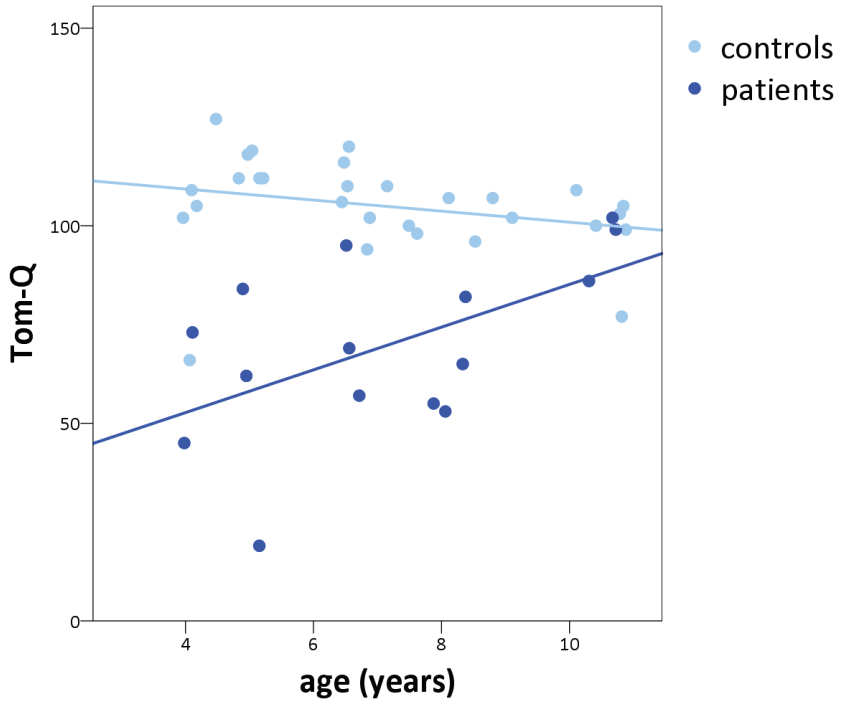

Figure 3.2: Relation between ToM-Q and age for patients and controls.

3.2 Epilepsy variables associated with ToM

In the group of patients, exploratory LMM analysis (Table 3.3) showed that epilepsy onset age and ToM-Q were significantly related: patients who were older at epilepsy onset obtained higher ToM-Q's. Also, patients with epilepsy and surgery restricted to the temporal area had higher ToM-Q's than children who underwent extra-temporal surgery or hemispherotomy (Table 3.3). Furthermore, differences between the assessments before and after surgery were not statistically significant. Relations between ToM-Q and the other illness variables (left or right side of epilepsy/surgery, resection of amygdala, etiology, AED number and seizure freedom) were not significant.

LMM analysis narrowed down to those variables that existed from the first epileptic seizure (onset age, side, area, etiology and implication of the amygdala) revealed that, apart from age at onset and surgical area, implication of the amygdala was related to ToM-Q: children whose amygdala was not included in the surgery obtained higher ToM-Q's (Table 3.4). Again, the relations between ToM-Q and time (pre-, 0.5, 1 and 2 years after surgery), between ToM-Q and the side of the resection, and between ToM-Q and etiology were not significant.

Table 3.3: LMM analysis of ToM-Q with time (in years), side of surgery, surgical area, status amygdala, etiology, AED number, seizure freedom and age at epilepsy onset (in years)

	Estimate	95% CI		F	df	p
Intercept	71.4	42.9	100	22.065	21.53	**< .001**
Time*	0.96	-8.07	9.99	.049	20.14	.827
Side surgery[a]	-10.7	-27.5	6.07	2.680	5.05	.162
Amygdala status[b]	33.9	-0.98	68.7	5.369	6.73	.055
Area surgery[c]	-30.62	-53.8	-7.49	10.694	5.77	**.018**
Etiology[d]				1.460	5.68	.321
Cerebral tumor	-32.1	-75.3	11.0			
MCD	-19.2	-56.6	18.1			
HS	-18.0	-52.4	16.5			
AED number	-3.56	-10.5	3.33	1.083	45.31	.303
Seizure freedom[e]	4.01	-19.5	27.5	.176	5.95	.690
Epilepsy onset age	7.42	3.39	11.45	21.553	5.34	**.005**

CI = confidence interval.
* Time = presurgical and ½, 1 and 2 years post surgery.
[a] Statistics for right sided surgery; left is reference.
[b] Statistics for amygdala not resected; amygdala resected is reference.
[c] Statistics for 'not temporal only' resection; temporal only is reference.
[d] 'Other' is reference.
[e] Statistics for 'not seizure free'; seizure free is reference.
Bold = $p < 0.05$.

Table 3.4: LMM analysis of ToM-Q with time and illness variables: side of surgery, surgical area, status amygdala, etiology and epilepsy onset age (in years)

	Estimate	95% CI		F	df	p
Intercept	67.3	44.9	89.8	34.038	11.28	**.000**
Time*	3.53	-4.04	11.09	.994	14.38	.335
Side surgery[a]	-12.1	-27.2	3.07	3.618	6.72	.101
Amygdala status[b]	34.7	1.25	68.1	5.425	9.46	**.043**
Area surgery[c]	-34.9	-54.8	-15.1	17.747	6.57	**.005**
Etiology[d]				2.134	7.43	.180
Cerebral tumor	-32.1	-70.3	6.01			
MCD	-20.4	-55.2	14.4			
HS	-20.5	-47.6	6.7			
Epilepsy onset age	7.49	3.67	11.31	20.964	7.483	**.002**

CI = confidence interval.
* Time = presurgical and ½, 1 and 2 years post surgery.
[a] Statistics for right sided surgery; left is reference.
[b] Statistics for amygdala not resected; amygdala resected is reference.
[c] Statistics for 'not temporal only' resection; temporal only is reference.
[d] 'Other' is reference.
Bold = $p < 0.05$.

3.2.1 Additional analyzed relations

In order to interpret the results properly, it was necessary to further study the relations between some other variables. First, because age at onset was related to ToM-Q and because age at onset and age of the child are related, we analyzed the correlation between age at surgery and epilepsy onset age and found it to be strong (Pearson $r = 0.71$; $p < .001$).

Secondly, age at onset appeared to be related together with surgical area to ToM-Q and VIQ was also strongly related to ToM-Q. Therefore, we calculated VIQ and age at onset for the surgical areas separately. The 'temporal only' group had a mean VIQ of 96 (sd = 13) and a mean epilepsy onset age of 3.9 years (sd = 2.7), whereas the group of hemispherotomized children and children with extra-temporal surgeries had a mean VIQ of 69 (sd = 15) and a mean epilepsy onset age of 3.7 years (sd = 2.7).

4. Discussion

As hypothesized, children with refractory epilepsy had poorer ToM skills than healthy control children, which could not be explained by differences in VIQ, and ToM did not change after epilepsy surgery.

ToM was better in children with later epilepsy onset, in children with temporal surgery and in children whose amygdala was not included in the surgery.

4.1 Children with refractory epilepsy have a ToM deficit

It is not surprising that we found a ToM-Q deficit in children with refractory epilepsy, as even children with 'epilepsy only' (epilepsy in the benign end of the severity spectrum), have recently been shown to have a ToM deficit.[16,17] Controlling for verbal intelligence quotient (VIQ) did not eliminate this effect.

ToM-Q is an age-normed score and therefore expected to be stable over age. Our finding of a relationship between age at assessment and ToM-Q pertained to patients only and could be unraveled as an effect of age at epilepsy onset: children with later epilepsy onset had better ToM-Q's. Patients with early-onset epilepsy were assessed at a younger age; the correlation between age at assessment and age at onset was large (Pearson $r = 0.735$; $p = .002$). The relation between age at onset and ToM-Q was confirmed by the analysis in patients only, where ToM-Q was related to several illness variables as discussed below (sub 4.2).

4.2 Surgical treatment does not change ToM-Q

Our primary interest concerned the effects of epilepsy surgery on ToM. Arguably, the effect could be favorable if cessation of seizures and discontinuation of AED's entailed ToM to develop without further disturbance by epilepsy, or unfavorable if surgery posed a second risk for ToM development. Using the four assessment times as a variable, surgery per se turned out to not have a significant effect on ToM-Q. This is in contrast to what we previously reported, recognizing facially expressed emotions, which was – although transiently – indeed affected by surgery in the group of younger (age < 13 years) patients.[19] The two tasks, recognizing facially expressed emotions and ToM, share the requirement of interpreting pictured emotions. An important difference is, however, that the test of recognizing facially expressed emotions is a straightforward visual recognition task, whereas in the ToM Storybooks the verbally and pictorially presented context is pertinent to interpreting the emotions. Also, the ToM Storybooks go beyond recognizing emotions, as they require the interpretation of mental states. We contend that ToM is less vulnerable to surgery than emotion recognition, because the contextual enrichment and the child's active manipulation of the stimulus materials afford a more cognitive than perceptual problem analysis and response construction. Within the scope of this reasoning, another difference seems to be relevant. In the task of recognizing facially expressed emotions, each face is shown for three seconds only, whereas in the ToM tasks, the presentation time of the items is not limited and, hence, speed plays no role. A more in-depth analysis of the supposition that speed is (transiently) unduly affected by epilepsy surgery requires a chronometric approach.

When time and all epilepsy-related variables [i.e., epilepsy onset age, side of surgery, surgical area (i.e., source area of seizures and hence surgical area), resection of amygdala, etiology, AED-number, seizure freedom] were included in the analysis, surgical area and epilepsy onset age were significantly related to ToM-Q. Children with temporal lobe epilepsy performed better on ToM than children with frontal, centro-parietal, and hemispheric epilepsy. This difference could not be explained by age differences or by a difference in age at onset between the groups. It may, however, be related to the level of general cognitive functioning, because the children with temporal surgery had a higher mean VIQ than the other groups (see Table 3.1).

Early epilepsy onset was associated with more deficient ToM-Q. Early onset age has often been reported as related to impaired cognitive functioning[26,27] and social cognition.[28] In her targeted review, Giovagnoli discussed the impact that epilepsy may have on ToM's underlying neural circuitry. She suggested that patients with early onset epilepsy are at an increased risk of either losing or not developing ToM abilities.[29] It might be argued

that early onset implicates more or earlier brain damage, that this affects the neural networks involved in ToM from the beginning and that this has an ongoing negative effect during development. There may be an effect of environment as well. Early onset implies early parental worries about the child, early special interactions with the child, and early epilepsy-related restrictions imposed upon the child.[30] It seems a viable and testable assumption that children with a history of refractory epilepsy have less opportunity to participate in social interactions with peers and others, and therefore develop the abilities to attribute emotions and mental states such as intentions, beliefs and desires to others and to one-self to a lesser degree than healthy peers.[31] That ToM-Q did not normalize after surgery could mean that the follow-up time of two years was too short for the patients to accumulate enough new social experiences to catch up on their ToM functioning, but could also mean that catch-up will not occur.

Trying to better understand the cerebral mediation of ToM, in particular the much-debated role of the amygdala, we noticed that onset age and surgical area – the two significant variables in our comprehensive analysis – both were treatment-independent. Excluding treatment variables (AED number and seizure freedom) from the LMM analysis revealed the significance of the implication of the amygdala. Children whose amygdala was not included in the resection had a better ToM-Q than children whose amygdala was resected (hence, in whom the epileptogenic zone had comprised the amygdala). Visual scrutiny of the data showed that both of the two temporally operated children without resection of the amygdala performed better on ToM than the four children in whom the temporal intervention had included the amygdala. The child who had undergone a hemispherotomy performed worse on ToM than the eight other children who had undergone extra-temporal surgery (see Supplementary Graphs S3.1 & S3.2).

Research on the role of the amygdala in ToM has yielded contradictory findings. Spunt et al., finding unimpaired ToM in adult patients with bilateral amygdala lesions, concluded that the amygdala is not necessary for the cortical mediation of ToM in adulthood.[32] In contrast, Stone et al., in a case study, argued that the amygdala continues to play a critical on-line role in ToM after the development of this ability.[33] Shaw et al., finding that early (i.e., prior to the age of 16 years) but not late damage to the amygdala impairs ToM, postulated that the amygdala may be necessary for low-level or proto-tasks such as recognizing facially expressed emotions but may not be a core component of the neural systems supporting the development of ToM-reasoning.[13] Although based on small numbers, the present contribution might be that inclusion of the amygdala in the surgical resection (meaning that the amygdala may have been affected by the epilepsy or the underlying etiology already before the surgery) has a negative effect on ToM in children.

Limitations and strengths

The population of children who undergo epilepsy surgery is heterogeneous with regard to variables such as age, intelligence, etiology and side and site of the surgery. This heterogeneity is reflected in our sample. Furthermore, the sample is small, which partly has to do with the age range for which ToM assessment instruments were available. However, research on ToM before and after epilepsy surgery in childhood has up till now not been reported. While readily admitting that replication of our findings in more homogeneous and larger cohorts and ideally with longer follow-up is necessary, we consider the systematic follow-up and the large and well-matched control sample as strengths of this countrywide study.

Rather than opting for a control group of children with a different chronic illness and/or a different (or no) surgical intervention, we recruited healthy children as controls for two reasons. We wanted to evaluate ToM in patients against a background of typical development, and we were aware that comparison with clinical groups would entail unwanted influences of illness-specific sets of variables. It is a methodological strength that two age- and sex-matched control children per patient were recruited from diverging social strata.

Conclusion

ToM appears to be vulnerable to variables that exist at the origin of the epilepsy, such as the cerebral area (rather than the side) of the epileptic focus and the onset age. The development of ToM is threatened by these variables, but barely influenced by treatment (whether surgery, anti-epileptic drug use or achieving seizure freedom). This renders eventual ToM-functioning of the children at least to some extent predictable before epilepsy surgery.

At any rate, we can try and help patients and their parents by educating them about possible consequences of epilepsy for developing social cognition. Parents can be helped to provide their children with the social vocabulary pertinent to participating in various social situations. In this way, children will be stimulated to practice perceiving and labeling their own emotions and thoughts as well as those of others, which may improve their ToM abilities.[31]

Highlights

- Children with refractory epilepsy have poorer ToM than controls.
- Epilepsy surgery does neither worsen nor improve ToM functioning.
- Higher epilepsy onset age is related to better ToM than younger onset age.
- Temporally located epilepsy is related to better ToM than extra-temporal epilepsy.
- The relation between ToM and implication of the amygdala needs further study.

Acknowledgments

Participation of the patients is gratefully acknowledged, as is participation of the control children and their parents. We also thank the schools that allowed us to acquire a control group of participants.

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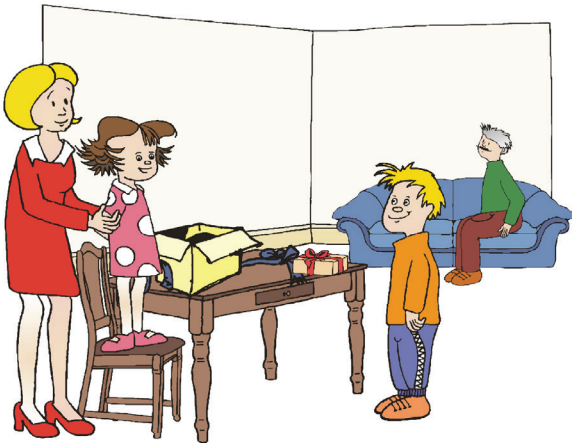
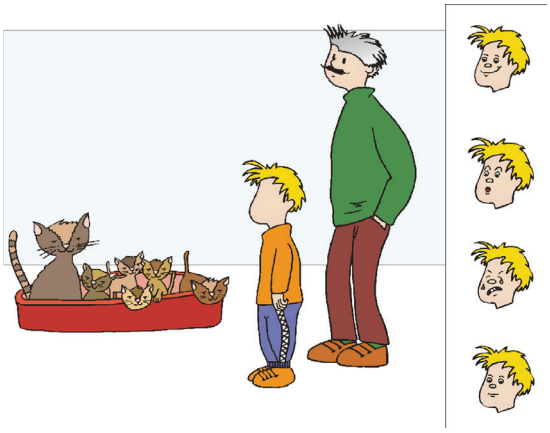
Appendix 3.1

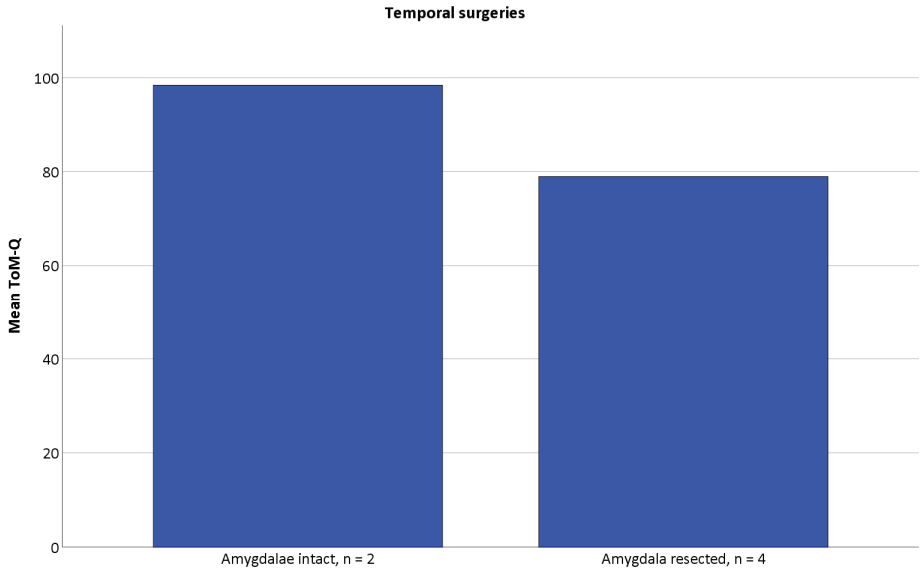


It's Sam's birthday. His sister may look in the box. Sam can only touch the box. Who knows what is in the box?

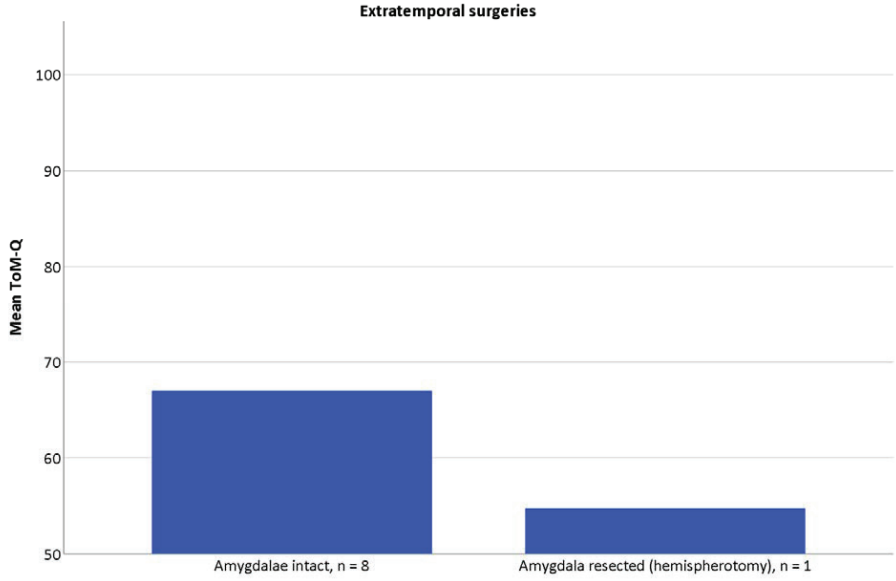


Sam is at his uncle who has kittens. Sam wants to take a kitten home. Daddy says they can't. How will Sam look?

Supplementary data



Supplementary Graph S3.1: Mean ToM-Q in temporally operated children, separated for resection or preservation of the amygdala.



Supplementary Graph S3.2: Mean ToM-Q in extra-temporally operated children, separated for resection or preservation of the amygdala.

Supplementary Table S3.1: LMM analysis of VIQ with time (in years), side of surgery, surgical area, status amygdala, etiology, AED number, seizure freedom and age at epilepsy onset (in years)

	Estimate	95% CI		F	df	p
Intercept	77.71	59.34	96.18	132.15	12.28	**< .001**
Time*	0.22	-0.16	0.60	1.44	20.74	.244
Side surgery[a]	12.08	0.96	23.19	8.09	4.72	**.039**
Amygdala status[b]	27.24	4.76	49.72	9.92	4.82	**.027**
Area surgery[c]	-39.14	-54.75	-23.54	34.74	7.23	**.001**
Etiology[d]				0.87	5.00	.517
Cerebral tumor	-12.11	-40.45	16.24			
MCD	-13.88	-38.11	10.34			
HS	-11.24	-34.13	11.66			
AED number	0.10	-3.47	3.69	0.00	34.55	.954
Seizure freedom[e]	4.67	-10.82	20.16	0.61	4.82	.470
Epilepsy onset age	0.01	0.002	0.02	11.19	4.86	**.021**

CI = confidence interval.
* Time = presurgical and ½, 1 and 2 years post surgery.
[a] Statistics for right sided surgery; left is reference.
[b] Statistics for amygdala not resected; amygdala resected is reference.
[c] Statistics for 'not temporal only' resection; temporal only is reference.
[d] 'Other' is reference.
[e] Statistics for 'not seizure free'; seizure free is reference.
Bold = $p < 0.05$.

Supplementary Table S3.2: LMM analysis of VIQ with time and illness variables: side of surgery, surgical area, amygdala status, etiology and epilepsy onset age (in years)

	Estimate	95% CI		F	df	p
Intercept	82.77	69.53	96.01	333.03	7.04	**< .001**
Time*	0.20	-0.12	0.53	1.84	14.00	.196
Side surgery[a]	13.00	3.67	22.35	10.85	7.00	**.013**
Amygdala status[b]	26.51	6.87	46.17	10.18	7.00	**.015**
Area surgery[c]	-39.27	-51.52	-27.01	57.43	7.00	**< .001**
Etiology[d]				2.39	7.00	.154
Cerebral tumor	-15.51	-38.41	7.40			
MCD	-17.14	-37.60	3.31			
HS	-16.25	-33.03	0.54			
Epilepsy onset age	0.01	.002	.015	10.81	7.00	**.013**

CI = confidence interval.
* Time = presurgical and ½. 1 and 2 years post surgery.
[a] Statistics for right sided surgery; left is reference.
[b] Statistics for amygdala not resected; amygdala resected is reference.
[c] Statistics for 'not temporal only' resection; temporal only is reference.
[d] 'Other' is reference.
Bold = $p < 0.05$.

Chapter 4

Personality traits of children before and after epilepsy surgery

Olga Braams, Renske Schappin, Joost Meekes, Peter van Rijen, Onno van Nieuwenhuizen, Kees Braun, Aag Jennekens-Schinkel

Epilepsy Res 2017;133:10-12

Abstract

We studied how children with epilepsy (CwE) who are candidates for epilepsy surgery, perceive themselves with respect to overarching personality traits and whether the traits change after surgery. We explored influences of demographic and illness variables. A total of 23 CwE [mean age at inclusion 12.8 (sd 2.3); 12 girls] participated. Using the Dutch Personality Questionnaire Juniors (DPQ-J), we assessed 20 of the CwE shortly before epilepsy surgery and compared the results to those of 39 age- and gender-matched healthy controls. Furthermore, we obtained follow-up scores 6, 12 and 24 months after epilepsy surgery from the clinical group. CwE who were candidates for epilepsy surgery scored above average in inadequacy, perseverance, social inadequacy and recalcitrance, whereas healthy peers scored average. Over the two years' period after epilepsy surgery we found no changes, apart from a decrease of social inadequacy. Sporadic illness and demographic variables were related to some personality traits. However, neither post-surgical seizure freedom nor cessation of AEDs did noticeably change the self-evaluations of CwE. Asking CwE to evaluate their personality themselves may offer a shared basis for individually tailored behavior intervention in order to help them adapting to their ameliorated circumstances after surgery.

1. Introduction

'I don't want them to look at me and think of my illness, I just want them to look at me and see me').[1] The citation is an urgent call for being recognized as a child who happens to have epilepsy, not as a patient with epilepsy.[2] Psychopathology rather than personality has been the focus of interest for children with epilepsy (CwE) and parents or clinicians performed the evaluations.[3, 4] The aim of the present study was to focus on how CwE perceive themselves with respect to overarching personality traits known as 'big five'.[5] This study has two main questions: do CwE who are candidates for epilepsy surgery differ from healthy peers in terms of personality traits? Do self-perceptions change during the two years after epilepsy surgery and if so, for which traits and in which direction? To answer these questions, CwE were assessed shortly before surgery (baseline) and 6, 12 and 24 months thereafter.

To better appreciate the pattern of personality traits, we explored associations with illness variables [epilepsy duration, surgical area, seizure freedom, number of anti-epileptic drugs (AEDs), the most frequently used AEDs in the study cohort (levetiracetam and carbamazepine)], demographic variables (age, gender), and time.

2. Methods

As part of a countrywide project addressing memory and social cognition CwE were consecutively included between January 2008 and December 2010.[6, 7] The Institutional Review Board of the University Medical Center Utrecht approved the study. Parents and children aged 12 years and older provided written informed consent.

2.1 Subjects

Twenty-three CwE (12 girls) participated. Ten had a glioneuronal tumor, eight a malformation of cortical development, four hippocampal sclerosis and one an old ischemic lesion. Prior to surgery, 20 CwE [mean age at baseline 13.4 (sd 1.9) years; mean verbal IQ (VIQ) 68 (sd 16); 10 girls] completed the questionnaire, as well as 39 healthy children, matched to the CwE for age [mean age 13.5 (sd 1.8)] and gender (20 girls) [mean VIQ 108 (sd 13)]. Due to age limits of the questionnaire (see 2.2), not every CwE participated in every assessment over the two-years' period.

2.2 Instruments

The DPQ-J ('Junior Nederlandse Persoonlijkheids Vragenlijst')[8] is a frequently used Dutch self-report questionnaire with good validity and sufficient reliability,[9] aimed at assessing broad personality traits known as 'big five' in children aged 9 to 16 years. The DPQ-J assesses *inadequacy*, *perseverance*, *social inadequacy*, *recalcitrance* and *dominance*. Raw scores are converted into 7-point scales ranging from 'very high' (7) through 'average' (4) to 'very low' (1). These qualifications solely indicate differences from the mean; a 'low' (or 'high') qualification may be adaptive in one situation and not in a different one. Intelligence was assessed simultaneously with personality, using a range of instruments (all with mean population score = 100) selected in conformity with the mandate of best clinical practice. Since reading and answering questions require verbal skills, the verbal intelligence quotient (VIQ) was used for analysis.

2.3 Data analyses

Statistical analyses were performed using IBM SPSS Statistics version 21.[10] Differences between CwE and controls at baseline were analyzed by means of multivariate analysis of variance (MANOVA), uncorrected and corrected for VIQ (Table 4.1). Linear mixed models (LMM) were used for the analysis across time, advantages of LMM over repeated measures ANOVA being their capacity to handle small samples, unequal time intervals between measurements, and missing scores. Time (prior to and 6, 12 and 24 months after surgery), age (per time point), VIQ (per time point), duration of epilepsy (years between onset and surgery) and number of AEDs (per time point), were included as covariates, and gender, surgical area (temporal or extratemporal), seizure freedom since surgery (yes/no, per time point), using levetiracetam (yes/no, per time point) and using carbamazepine (yes/no, per time point) as factors (Table 4.2). Because the sample was small and there were only four time points in the model, a random slope was not estimated and the covariance structure of the random intercept was scaled identity. P-values < 0.05 were considered to be statistically significant. Effect sizes (η^2) were considered small (> 0.01), moderate (> 0.06), or large (> 0.14).[11]

3. Results

Prior to surgery, CwE differed significantly from healthy peers on four of the five personality traits: inadequacy, perseverance, social inadequacy and recalcitrance (Table 4.1). The difference (η^2) was large for inadequacy and recalcitrance and moderate for perseverance and social inadequacy. CwE scored 'above average' (4.7–5.1) and controls

Table 4.1: Comparing personality trait scores of CwE and controls at baseline, uncorrected and corrected for VIQ

	CwE n = 20	Controls n = 39	MANOVA CwE versus Controls			MANOVA CwE versus Controls corrected for VIQ		
	mean (sd)	mean (sd)	F	p	η^2	F	p	η^2
Inadequacy	5.1 (1.5)	3.7 (1.6)	10.87	**.002**	.16	5.41	**.007**	.16
Perseverance	4.8 (1.6)	3.7 (1.4)	7.14	**.010**	.11	5.50	**.007**	.16
Social inadequacy	5.1 (1.7)	3.9 (1.8)	5.85	**.019**	.09	3.12	**.049**	.10
Recalcitrance	4.7 (1.6)	3.5 (1.2)	9.84	**.003**	.15	5.02	**.010**	.15
Dominance	3.8 (1.9)	4.2 (1.6)	0.87	.354	.02	0.84	.439	.03

MANOVA = multivariate analysis of variance; sd = standard deviation. $p < 0.05$ in **bold**.

'average' (3.5–3.9) on these four traits. The differences between CwE and controls remained significant after correction for VIQ (Table 4.1).

Follow-up analysis revealed a significant decrease on social inadequacy, and effects of gender on recalcitrance (boys scored higher than girls), of surgical area (children with temporal lobe surgery scored lower on social inadequacy than those operated upon in extratemporal areas) and of levetiracetam (children who used levetiracetam scored higher on social inadequacy than those who did not) (Table 4.2).

4. Discussion

Children who were candidates for epilepsy surgery scored higher than healthy peers on four of five overarching personality traits, i.e., inadequacy, perseverance, social inadequacy and recalcitrance. The differences remained after correction for VIQ. Over the two years' period after epilepsy surgery, only the social inadequacy score decreased. Visual inspection showed the decrease to be gradual over time. An exploratory search revealed sporadic effects of illness and demographic variables.

We presume that the differences with healthy peers are to a large extent the upshot of everyday experiences of CwE. CwE are known to experience excessive fatigue,[2] which limits their participation in after-school activities. Because seizures are unpredictable and may be harmful, CwE have to deal with several types of restrictions such as those related to swimming, riding a bike, playing outside, staying elsewhere overnight and going to parties.[12] Even during sleep some CwE are monitored. Such restrictions, together with

Table 4.2: Linear mixed model of demographic, illness- and time-related predictors of personality traits

	N (%) or mean (sd)	Inadequacy Estimate (se) p	Perseverance Estimate (se) p	Social Inadequacy Estimate (se) p	Recalcitrance Estimate (se) p	Dominance Estimate (se) p
Time of assessment		-0.02 (0.02) .159	-0.00 (0.02) .927	**-0.04 (0.02) .028**	0.01 (0.02) .731	-0.02 (0.02) .376
Gender						
Boys	11 (48%)	0.35 (0.60) .569	-1.01 (0.52) .067	-0.27 (0.63) .678	1.06 (0.45) .032	0.18 (0.67) .793
Age	mean 12.8y (2.3)	-0.09 (0.16) .563	-0.03 (0.14) .831	-0.11 (0.17) .514	-0.17 (0.12) .172	0.28 (0.18) .133
VIQ	mean 83 (17)	-0.02 (0.02) .401	-0.02 (0.02) .398	-0.02 (0.02) .415	-0.01 (0.02) .710	-0.02 (0.02) .498
Epilepsy duration	mean 6.3y (4.1)	-0.14 (0.09) .147	0.07 (0.08) .403	0.07 (0.09) .496	-0.06 (0.07) .386	-0.08 (0.10) .441
Area						
Temporal	9 (7 left, 2 right sided)	-1.07 (0.63) .111	-0.99 (0.54) .088	**-1.42 (0.67) .049**	-0.92 (0.34) .070	-1.36 (0.71) .070
Extratemporal	14 (9 left, 4 right sided*)	reference	reference	reference	reference	reference
Seizure freedom[a]	17 (74%)	-0.48 (0.35) .171	-0.21 (0.38) .587	-0.09 (0.31) .783	-0.30 (0.34) .390	0.30 (0.40) .454
Number AED[b]		0.05 (0.30) .879	0.07 (0.31) .814	-0.13 (0.28) .634	0.45 (0.27) .106	-0.06 (0.34) .869
1	6 (26%)					
2	11 (48%)					
3	5 (22%)					
4	1 (4%)					
Levetiracetam	7 (30%)	-0.06 (0.43) .884	-0.27 (0.46) .565	**0.92 (0.39) .022**	0.17 (0.42) .685	0.24 (0.49) .626
Carbamazepine	15 (68%)	-0.13 (0.42) .761	0.79 (0.44) .074	-0.39 (0.38) .314	-0.38 (0.39) .331	0.11 (0.48) .810
Random intercept		1.52 (0.72) .034	0.92 (0.48) .056	1.84 (0.75) .014	0.65 (0.39) .092	1.87 (0.81) .021

sd = standard deviation; se = standard error. $p < 0.05$ in **bold**.

* And one child with bilateral surgery.

[a] 17 children were seizure free since surgery at 24 months after surgery. In the LMM, seizure freedom since operation at each time point was analyzed.

[b] Number AED: the numbers (%) refer to AEDs used at pre-surgical assessment. In the LMM, AED number at each time point was analyzed.

having to use AEDs, affect autonomy development and self-perception of competence, particularly if seizures are pharmacoresistant.[13] Thus, it is not surprising that personality traits differ between CwE and healthy peers. That CwE perceive themselves as persevering may be understood from increased efforts to compensate for illness-related setbacks, e.g. missing lessons at school and fatigue. Inadequacy (having vague anxieties, low self-confidence and often depressed mood) can be fed by, e.g., shame because of the social effects of (unpredictable) seizures[14] and by insecurity caused by the seizures per se. Many CwE appraise emotions expressed by faces less well than healthy peers,[7] a disadvantage that may be related to retarded development of social skills, and may contribute to social inadequacy. Experiences of being excluded and attracting negative attention by one's incompetence in social interactions may be reflected in increased recalcitrance (an oppositional attitude towards others) and in the heartfelt cry for being treated as a normal child.[2]

Becoming seizure- and medication-free, bringing along a cessation of epilepsy-related restrictions in daily life, would conceivably provide the child with positive experiences that might change personality traits,[15] which was, indeed, the case for one personality trait: social inadequacy decreased. The lack of significant change in the remaining personality traits over the two years after epilepsy surgery suggests that neither the surgical intervention nor the change in epilepsy status influenced the personality traits strongly. Personality traits have, by definition, a certain amount of stability. Perhaps, having lived with epilepsy and epilepsy-related restrictions for a large part of one's life, requires a longer period of positive experiences to noticeably change personality. If the behavior tendencies represented by the trait are counter-adaptive, behavioral intervention may be envisaged in some cases to enable the children (and their surroundings) to cope with and adapt to ameliorated circumstances.[16] The present study underscores the importance to ask CwE themselves to evaluate their personality, as this may offer a shared basis for individually tailored behavior interventions.

The exploratory search revealed just a few demographic and epilepsy influences. Girls scored lower on recalcitrance than boys. Because of the well-known gender difference in recalcitrance, the DPQ-J offers separate norm tables for recalcitrance of girls and boys. Apparently, in CwE the disposition to recalcitrance of boys and girls differs more than in the general population, the origin of which needs to be studied further. The effects of extratemporal surgery and the use of levetiracetam on social inadequacy may be understood from changes in behavior related to frontal pathology and side effects of levetiracetam, but require further research.

4.1 Conclusions

Judged from their own self-perceptions, CwE tend to inadequacy, perseverance, social inadequacy and recalcitrance. After surgery, social inadequacy diminishes gradually. Post-surgical seizure freedom and cessation of AEDs do not noticeably change the other traits. Taking departure from self-perceived personality offers a shared basis for helping CwE to better adapt to their circumstances. The present results await replication in a larger sample of CwE, with longer follow-up.

Highlights

- CwE tend to inadequacy, perseverance, social inadequacy and recalcitrance.
- After surgery, social inadequacy diminishes.
- Seizure freedom and cessation of AEDs do not noticeably change the other traits.
- Self-perceived personality is a basis for helping CwE adapt to their circumstances.

Acknowledgments

Participation of all children and their parents is gratefully acknowledged.

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Part II

Parents

Chapter 5

Parenting stress does not normalize after child's epilepsy surgery

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Epilepsy Behav 2015;42:147-152

Abstract

Purpose: To investigate parenting stress expressed by parents before and two years after their children's epilepsy surgery.

Methods: *Subjects:* Parents of 31 consecutively included epilepsy surgery patients and of 31 healthy sex- and age-matched control children. *Materials and procedure:* The questionnaire 'Parenting Stress Index', which distinguishes a Parent domain (stress leading parents to feel themselves inadequate) and a Child domain (child features felt by parent to cause stress) was completed before surgery of the patients and two years thereafter. At both time points, intelligence examination of the child was part of a comprehensive neuropsychological assessment, as were evaluations of recent stress-enhancing life events and epilepsy severity.

Results: Prior to surgery, total parenting stress was significantly higher in parents of patients than in parents of controls. Two years after surgery, total parenting stress had decreased significantly in parents of patients. The scores on parent-related subscales Role Restriction and Spouse and on the child-related subscale Distractibility/Hyperactivity, all relatively high before surgery, decreased significantly. Still, parents of patients experienced significantly more stress than control parents, mainly due to persistently higher stress scores in parents of patients on the subscale Role Restriction (Parent domain) and on five of six subscales in the Child domain. Intelligence of the child was associated with parenting stress: the lower the child's intelligence, the higher the stress score on the subscale Distractibility/Hyperactivity and the lower on the subscale Mood. Stress decreased more in parents of patients who became seizure free after surgery than in parents of patients with recurrent seizures.

Conclusions: Parenting stress decreases but does not normalize in the first two years after epilepsy surgery. Parents should be offered counseling on epilepsy-related intricacies contributing to parenting stress, immediately after diagnosis as well as after epilepsy surgery, notwithstanding the resulting seizure status of the child.

1. Introduction

Parenting-related stress is since long acknowledged as an important determinant of dysfunctional parenting.[1,2] Dysfunctional parenting affects the child's behavior, the latter affects parenting stress and the increased parenting stress increases dysfunctional parenting.[3] Current models of parenting stress, i.e., of 'the aversive psychological reaction to the demands of being a parent', agree that complex processes underlie parenting stress.[1-3] Testing and cross-validating their multidimensional model of parenting stress, Östberg and Hagekull demonstrated a pattern of direct and indirect effects on parenting stress in mothers of infants and pre-school children. Everyday problems with, e.g., feeding and sleeping, excessive crying and illness were among the direct contributors to mothers' parenting stress.[2] Irregularity of the child's rhythmicity in biologically determined needs contributed indirectly to mothers' parenting stress, i.e. through her perceiving the child as fussy or difficult.[2]

Parents of a chronically sick or handicapped child are at increased risk of parenting stress, as the presence of such a child places considerable (extra) physical and emotional strain on parents (as well as on healthy siblings and even extended relations).[4] Childhood epilepsy, and particularly pharmacologically intractable epilepsy, is a risk factor par excellence for parenting stress.[5-10]

However, data on the severity of parenting stress in parents of children with epilepsy vary widely. Explanations for the disparate estimates are as yet unclear. At one month after diagnosis, parents of children with new onset epilepsy could not be distinguished from parents of healthy control children on generic and epilepsy-specific parenting stress scales.[7] Importantly, the children whose parents participated in that study[7] had been developing normally until the diagnosis. So, the course or severity of the epilepsy appears to be important, as markedly increased parenting stress has been reported in mothers with children suffering from pharmacologically intractable epilepsy who were on a ketogenic diet, were treated with vagal nerve stimulation, or with unsuccessful epilepsy surgery.[8]

If candidates are carefully selected, epilepsy surgery, which aims at removing the cause of the seizures, is a successful treatment for pharmacological intractable epilepsy in childhood.[11] We are not aware of any study that compared parenting stress before and after epilepsy surgery in children. Ideally, cessation of seizures and usually also tapering off anti-epileptic medication after successful surgery will decrease parenting stress. However, our clinical impression is that parenting stress can also persist, probably due to cognitive and behavioral comorbidities which in most cases remain after epilepsy surgery. In fact, despite successful surgery, parenting stress may even increase. For instance, parents who

fostered unrealistic expectations with respect to their child's cognitive and behavioral functioning after the surgery may be disappointed, and may experience increased stress. Alternatively, cessation of the seizures may deprive parents of certain rewards derived from the medical care and close attention that had been offered when managing their child's epilepsy. After unsuccessful surgery, disappointment and grief and of course the necessity of continued specialized care may be at odds with decrease of parenting stress. It is, however, equally possible that parents, feeling that they have done everything that was medically possible, resign to the situation and may experience a decrease of stress.

The main purpose of the present study was to know whether epilepsy surgery in children influences parenting stress, and if so to what extent. We compared parenting stress in parents of patients before and two years after epilepsy surgery with that in parents of healthy matched control children at baseline and two years later. Finally, we explored associations between parenting stress in parents of patients and the following variables: time (baseline versus two years later); post-surgical seizure status (seizure freedom versus seizure recurrence); severity of the seizures prior to surgery as estimated by the parents (on the assumption that the degree of severity influences the burden of every day care) and the child's intelligence level prior to surgery (because the child's cognitive development is a major factor in parenting).[12,13] To ensure that the effects of these variables were not attributable to other variables, such as age at surgery, gender of the patient, number of stress enhancing life-events and education and occupational status of the parents, we checked the relationships of the latter with parenting stress.

2. Methods

2.1 Design

The study was part of a countrywide project addressing the effects of epilepsy surgery on cognitive, affective and psychosocial functioning in children.[14,15] Parenting stress was examined shortly before epilepsy surgery (baseline) of the patients and two years thereafter (follow-up). The two years' follow-up was chosen because by this time, in many children anti-epileptic drugs have (almost) been tapered off, seizure-related visits to outpatient departments have reduced or stopped, and the parents have had time to adapt to their child's new – mostly seizure-free – condition. Control parents participated with the same time interval.

2.2 Subjects

Recruitment took place between January 2008 and December 2010. As soon as the Dutch Collaborative Epilepsy Surgery Programme (DuCESP) had accepted a child as a candidate for epilepsy surgery, the neurologist introduced the project to the parents and, if relevant, to the child, after which we sent the parents a written request to participate. Upon reception of the agreement to participate, age- and gender-matched control children were recruited. Parents of 46 patients fulfilled the requirement of the present study (child's age range from two to 16 years at inclusion). Parents of four patients did not return the questionnaires. Excluded was one parent whose Dutch reading skills were insufficient to complete the questionnaires. Two more parents were excluded because their children were re-operated on within the follow-up time. In four cases it was not the same parent who completed the questionnaire before and after surgery, rendering the comparison of perceived stress with respect to their child unreliable. As this was also the case in four control parents, four more parents of patients had to be excluded. Data obtained from the parents (29 mothers) of 31 patients [mean age at first assessment 8.5 years, standard deviation (sd) 4.2 years; 13 girls; average intelligence 65 (sd 22) prior to surgery and 71 (sd 26) two years thereafter], were analyzed. Group-wise, participating and non-participating parents did not differ in terms of their children's intelligence level (IQ), gender and age at surgery. Thirteen patients attended regular schools, 12 received special education and six children were too young for compulsory education. Data from 31 parents (29 mothers, 2 fathers) of healthy children matched for age and gender to the patients [mean age at first assessment 8.4 (sd 4.1) years] allowed us to compare parenting stress in parents of patients with that in parents of healthy children and to control for re-test effects. The control children [mean IQ 108 (sd 18) at baseline and 117 (sd 16) two years later] had no history of neurological disease, were recruited from regular schools located in affluent and less affluent neighborhoods and participated at a similar time interval as did the patients. All patients and control children were living at home with their family. The Institutional Review Board of the University Medical Center Utrecht had approved of the study. Parents of all children and also all children above the age of 12 years provided written informed assent.

2.3 Instruments

2.3.1 The Parenting Stress Index (PSI)

The Parenting Stress Index (PSI) adapted for The Netherlands (Nijmeegse Ouderlijke Stress Index) measures psychological stress arising from parenting.[16,17] The self-report questionnaire is normed for parents of children in the age range of two to 16 years. When

completing the questionnaire, the parent has to focus on one and the same child, so that a measure of child-specific rather than general parenting stress is obtained. Separating a Child domain (six subscales) and a Parent domain (seven subscales), the instrument allows one to discern whether the stress is related to the parent feeling unfit for the task of parenting this child or to particular features of this child (see Appendix 5.1). The PSI consists of 123 items referring to how parents experience their child's behavior and their own functioning within the family. The parents respond on six-point Likert-type scales ('fully agree' to 'fully disagree'). Raw scores are converted to seven-point Likert-type standard stress scores ranging from very low (scale value 1) to very high (scale value 7) with mean scale value 4. Test construction, concept validity and criterion validity of the Dutch PSI-adaptation are described as good, and its reliability as adequate.[18]

2.3.2 Added to the PSI is the Life Stress Scale

This checklist addresses stress-enhancing life events in the last six months with respect to family (17 items), work (5 items), financial situation (4 items), health (6 items) and miscellaneous other topics (8 items).

2.3.3 The Hague Seizure Severity Scale (HASS)

The Hague Seizure Severity Scale (HASS) completed by the parents at pre-surgical neuropsychological assessment and two years after surgery quantifies, by means of four- or five-point scales, 13 ictal and post-ictal problems that may have been encountered in the three previous months. The scale is based on the Liverpool Seizure Severity Scale,[19] with modifications to allow completion by parents and with incorporation of child-relevant items; the selection of the latter items followed item- and content analysis. Test-retest stability and internal consistency of the HASS have been described as sufficient.[20] Scores vary between no (zero) to maximal (55) epilepsy-related problems.

2.3.4 Intelligence

Intelligence or – for very young or developmentally delayed children – mental development of the child was assessed using a range of instruments, selected in conformity with the mandate of best clinical practice (e.g., WISC-III, BSID-II). The score will be referred to as 'intelligence'. For the two children who scored below the lowest norm value, intelligence was calculated (100 * mental age / calendar age). Intelligence examination of the child was part of a comprehensive neuropsychological assessment.[14,15]

2.4 Data management and analyses

Statistical analysis was performed using IBM SPSS Statistics version 20.21 Pre- and postoperative group differences and changes in stress were studied with three separate multivariate analyses of variance (MANOVA). Post-hoc univariate tests revealed the subscales that were significantly affected by the independent variable. P-values < 0.05 were considered statistically significant. Effect sizes (η^2) were considered small (> 0.01), moderate (> 0.06) or large (> 0.14).[22]

3. Results

3.1 Baseline parenting stress: differences between parents of patients and control parents

Mean parenting stress scores at baseline and after two years were calculated for the two groups (parents of patients and control parents) (Table 5.1, first measurement). Parents of children with epilepsy expressed more than average parenting stress (defined as standard score > 4.5) on two subscales in the Parent domain (Role Restriction and Spouse) and three in the Child domain (Distractibility/Hyperactivity, Demandingness and Acceptability).

Parents of patients differed significantly from control parents: multivariate $F(13, 48) = 5.05$, $p < 0.001$, $\eta^2 = 0.578$. Parents of patients expressed significantly more stress on three of seven subscales in the Parent domain (Role Restriction, Health and Spouse) and on all subscales in the Child domain (Adaptability, Mood, Distractibility/Hyperactivity, Demandingness, Reinforces Parent and Acceptability) (Table 5.1, first measurement).

3.2 At follow-up after two years: differences in parenting stress between parents of patients and control parents

At reassessment, mean parenting stress in parents of patients still differed significantly from that in parents of healthy controls: multivariate $F(13, 48) = 2.92$, $p = 0.003$, $\eta^2 = 0.441$. The difference was mostly due to more stress in parents of patients than in control parents on two subscales in the Parent domain (Role Restriction and Social Isolation) and on all subscales but one (Reinforces Parent) in the Child domain (for statistics, see Table 5.1, follow-up measurement).

Table 5.1: Parenting Stress Index (PSI) scores [mean (standard deviation, sd)] in parents of patients before and two years after surgery, in parents of controls at similar time points and change (Δ) between the measurements in parents of patients

	First measurement					Follow-up measurement					Change of stress (Δ)			
Subscale	Parents of patients	Parents of controls	F	p	η^2	Parents of patients	Parents of controls	F	p	η^2	Parents of patients	F	p	η^2
Parent domain														
Competence	2.74 (1.63)	2.16 (1.51)	2.117	0.151	0.034	2.81 (1.83)	2.19 (1.47)	2.109	0.152	0.034	0.07	0.088	0.768	0.003
Role restriction	5.13 (1.13)	3.84 (1.68)	11.412	**0.001**	0.160	4.19 (1.97)	3.10 (1.56)	5.902	**0.018**	0.090	-0.94	13.154	**0.001**	0.305
Attachment	3.32 (1.18)	2.84 (1.55)	1.590	0.212	0.026	3.06 (1.65)	2.52 (1.69)	1.669	0.201	0.027	-0.26	0.775	0.386	0.025
Depression	3.23 (1.18)	3.00 (1.34)	0.232	0.632	0.004	2.81 (1.38)	2.65 (1.38)	0.212	0.647	0.004	-0.42	4.024	0.054	0.118
Health	4.10 (1.40)	2.97 (1.96)	6.748	**0.012**	0.101	3.68 (1.62)	2.97 (1.74)	2.759	0.102	0.044	-0.42	1.912	0.177	0.060
Social isolation	4.13 (1.71)	3.45 (1.34)	3.023	0.087	0.048	3.65 (1.76)	2.68 (1.82)	4.539	**0.037**	0.070	-0.48	3.416	0.074	0.102
Spouse	4.68 (1.45)	3.71 (1.32)	7.563	**0.008**	0.112	3.94 (1.97)	3.52 (1.75)	0.788	0.378	0.013	-0.74	8.007	**0.008**	0.211
Child domain														
Adaptability	4.10 (1.49)	2.77 (1.38)	13.106	**0.001**	0.179	4.00 (2.02)	2.65 (1.72)	8.087	**0.006**	0.119	-0.10	0.135	0.716	0.008
Mood	3.74 (1.59)	2.77 (1.56)	5.832	**0.019**	0.089	3.71 (2.19)	2.45 (1.41)	6.846	**0.011**	0.102	-0.03	0.012	0.914	0.000
Distractibility/ Hyperactivity	5.29 (1.13)	3.68 (1.19)	29.809	**< 0.001**	0.332	4.58 (1.31)	3.65 (1.23)	8.421	**0.005**	0.123	-0.71	7.508	**0.010**	0.200
Demandingness	5.26 (1.69)	2.74 (1.37)	41.501	**< 0.001**	0.409	4.84 (2.13)	2.52 (1.57)	23.897	**< 0.001**	0.285	-0.42	1.324	0.259	0.042
Reinforces parent	3.84 (1.66)	3.03 (0.98)	5.441	**0.023**	0.083	3.61 (1.71)	3.03 (1.17)	2.443	0.123	0.039	-0.23	0.826	0.371	0.027
Acceptability	4.87 (1.50)	2.52 (1.39)	41.182	**< 0.001**	0.407	4.52 (1.96)	2.61 (1.50)	18.399	**< 0.001**	0.235	-0.35	1.258	0.271	0.040

P-values < 0.05 (in **bold**) were considered statistically significant. Effect sizes (η^2) were considered small (> 0.01), moderate (> 0.06) or large (> 0.14).[22]

3.3 Changes (Δ) of parenting stress in parents of patients and in control parents

Parenting stress changed significantly in parents of patients and in control parents taken together: multivariate $F(13,48) = 2.47$, $p = 0.011$, $\eta^2 = 0.401$. The two groups did not differ significantly in the amount of change: $F(13,48) = 0.81$, $p = 0.649$, $\eta^2 = 0.180$. Increase of stress did not occur. Decrease was significant on four of seven subscales in the Parent domain (Role Restriction: $F = 17.013$, $p < 0.000$, $\eta^2 = 0.221$; Depression: $F = 5.193$, $p = 0.026$, $\eta^2 = 0.080$; Social Isolation $F= 13.997$, $p < 0.000$, $\eta^2 = 0.189$; Spouse: $F = 7.347$, $p = 0.009$, $\eta^2 = 0.109$) and on one of five subscales in the Child domain (Distractibility/Hyperactivity: $F = 5.604$, $p = 0.021$, $\eta^2 = 0.085$).

3.4 Predictors of stress in parents of patients

We explored associations of parenting stress and its change, with seizure status, parental estimations of seizure severity prior to surgery, and intelligence of the child prior to surgery; only intelligence predicted parenting stress: $F(13,15) = 4.273$, $p = 0.004$, $\eta^2 = 0.787$ and only seizure status predicted change in parenting stress: $F(13,15) = 2.953$, $p = 0.024$, $\eta^2 = 0.719$. Table 5.2 shows mean stress scores, mean parental estimations of seizure severity and mean intelligence scores of the children, separately for seizure-free patients and patients with seizure recurrence.

Post-hoc analyses showed significant effects of intelligence on parenting stress for two subscales, both in the Child domain: Mood ($F = 4.222$, $p = 0.050$, $\eta^2 = 0.135$) and Distractibility/Hyperactivity ($F = 10.624$, $p = 0.003$, $\eta^2 = 0.282$). Inspection of the data suggested that the lower the intelligence of the child was, the higher was the parenting stress score on the subscale Distractibility/Hyperactivity and the lower on the subscale Mood.

The effect of seizure status on change of stress was significant for the subscale Role Restriction in the Parent domain ($F = 8.217$, $p = 0.008$, $\eta^2 = 0.233$): stress related to Role Restriction decreased more in parents of seizure-free patients than in parents of patients with recurrent seizures.

4. Discussion

This is to the best of our knowledge the first study of changes in parenting stress, experienced by parents of children who had epilepsy that was surgically treated. Shortly before epilepsy surgery, parents of children with epilepsy experienced more parenting stress than those of healthy peers. Two years after successful epilepsy surgery in their child,

Table 5.2: Parenting Stress Index (PSI) scores [Means (standard deviations, sd)] and scores [Means (sd)] of predictive variables intelligence and parent-perceived seizure severity before and two years after surgery, shown separately for parents of seizure-free patients and parents of patients with recurrent seizures

	Before surgery		Two years after surgery	
Subscale	Parents of seizure-free patients (n = 21) Mean (sd)	Parents of patients with recurrent seizures (n = 10) Mean (sd)	Parents of seizure free patients (n = 21) Mean (sd)	Parents of patients with recurrent seizures (n = 10) Mean (sd)
Parent domain				
Competence	2.52 (1.69)	3.2 (1.48)	2.48 (1.86)	3.5 (1.65)
Role restriction	4.90 (1.30)	5.6 (1.27)	3.57 (1.94)	5.5 (1.35)
Attachment	3.29 (1.45)	3.4 (1.58)	2.76 (1.55)	3.7 (1.77)
Depression	2.90 (1.26)	3.7 (1.25)	2.62 (1.24)	3.2 (1.62)
Health	3.76 (1.41)	4.8 (1.14)	3.52 (1.47)	4.0 (1.94)
Social isolation	3.81 (1.63)	4.8 (1.75)	3.29 (1.65)	4.4 (1.84)
Spouse	4.71 (1.31)	4.6 (1.78)	3.81 (1.99)	4.2 (1.99)
Child domain				
Adaptability	3.81 (1.60)	4.7 (1.06)	3.52 (1.97)	5.0 (1.83)
Mood	3.43 (1.60)	4.4 (1.43)	3.24 (2.10)	4.7 (2.16)
Distractibility/Hyperactivity	5.19 (1.17)	5.5 (1.08)	4.57 (1.40)	4.6 (1.17)
Demandingness	5.14 (1.56)	5.5 (2.01)	4.29 (2.08)	6.0 (1.83)
Reinforces parent	3.62 (1.27)	4.3 (1.70)	3.19 (1.54)	4.5 (1.78)
Acceptability	4.62 (1.24)	5.4 (1.90)	4.19 (2.02)	5.2 (1.75)
Predictive variables	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Intelligence	69 (20)	55 (24)	78 (25)	56 (22)
Seizure severity	33.2 (9.2)	29.2 (12.5)	0 (0)	25.7 (13.9)

parents expressed less parenting stress than before, but still more than control parents. Parenting stress was influenced by post-surgical seizure status and intelligence of the child.

4.1 Prior to surgery

Parents of children with epilepsy expressed more than average parenting stress on five subscales. Two of these scales, Role Restriction and Spouse, are part of the seven subscales constituting the so-called Parent domain, which reflects feeling inadequate for one's parenting task. This may be understood from the fact that seizures are in the majority of cases unpredictable, which induces uncertainty in parents[6] and a tendency to watch their child all the time to ensure his safety. Also, the feeling that fatigue and stresses and strains in the child may induce seizures[23] renders many parents less eager to go on family

trips with this child, let alone to undertake spontaneous activities with this child or go out together and leave the child with a sitter. Presumably, this continuous protecting is felt by the parents to restrict their role, their freedom of movement. With respect to the subscale Spouse, it is known that children with a chronic illness put high pressures on marital relationships.[24] Spouses often cope differently with their worries about the child and have different thoughts on how to raise the child with the chronic illness (and, for that matter, the healthy siblings). All this can make a parent feel to lack factual and emotional support by the spouse.

The three other subscales on which parents of children with epilepsy expressed undue stress are Demandingness, Distractibility/Hyperactivity and Acceptability. These subscales are part of the Child domain, which reflects the contribution of particular child features (as felt by the parent) to the parent's overall stress experience. Demandingness taps the degree to which parents feel that the child calls for their attention, for example by crying a lot, claiming attention and asking for help. Östberg and Hagekull demonstrated the influence of caretaking problems on parenting stress.[2] Seizures render children more than healthy peers dependent on their parents for their safety and comfort, which increases the parental burden. Acceptability taps the degree to which the parent experiences the child as satisfying her/his expectations. The increased score on this subscale may express parental difficulty accepting the peculiarities, such as fussiness or difficultness, as described as a temperamental variable but indeed a feature that frequently goes together with epilepsy.[2] The increased score on Acceptability may also reflect difficulty to accept comorbidities of epilepsy, such as developmental, behavioral and social abnormalities.[25] Distractibility/Hyperactivity taps the degree to which parents experience their child as being overactive and easily distracted. In their meta-analysis of psychopathology in children with epilepsy, Rodenburg et al. signaled an overrepresentation of attention problems in children with epilepsy.[26] The evidence for favorable effects of pharmacological treatment of Attention Deficit and Hyperactivity Disorder (ADHD) in children and young people with severe epilepsy[27] pleads for considering medication to support managing these behavioral problems.

Using the same instrument as we did, the PSI, Wirrell et al.[9] found a parenting stress pattern similar to the one presently reported, with at first sight one difference. The lowest average stress score in the Child domain in their study concerned Distractibility/Hyperactivity, which scored highest in the present study. Differences between the two study groups may contribute to this apparently contradictory finding. The study by Wirrell et al. pertained to patients whose epilepsy precluded epilepsy surgery or was surgically treated with insufficient success. Indeed, almost half of the children in the study by Wirrell

et al.[9] had a severe cognitive impairment (IQ < 40) as against only three percent (one child) in the present study. It should be noticed that Wirrell et al.[9] reported average raw scores and percentages of clinical scores whereas we used standard scores.

4.2 At follow-up: two years after surgery

Epilepsy surgery achieves seizure freedom in the majority of cases. It also lowers parenting stress, but not to normal levels. That cessation of the seizures has a positive effect on parenting stress, may be understood from the fact that uncertainty with respect to seizure occurrence has disappeared, but perhaps also that caretaking intensity and the child's rhythmicity have normalized or at least ameliorated.[2] However, important comorbidities that are known in patients with severe epilepsy, such as cognitive disabilities and impairment of psychosocial functioning, usually remain or do not drastically improve after epilepsy surgery. Hence, it may not be surprising that parenting stress remains relatively high two years after the child's epilepsy surgery.

4.3 Changes in stress after surgery

Parenting stress decreased in parents of patients, but – contrary to our expectation – overall not more or less than in control parents. Searching for an explanation, we found that, in control parents, age of the child was significantly but inversely related with parenting stress (data not shown): parents of younger healthy children expressed more stress than those of older ones. This correlation was significant for the subscales Role Restriction and Social Isolation. Normally, growing older goes hand in hand with increasing independence. The association between age of the child and parenting stress was not found in parents of patients. Epilepsy limits children in the development of age-appropriate independence.[5] Both subscales seem to reflect that increasing independence of the child lowers parenting stress. The proposal that independence is pivotal for both subscales (as perhaps for other subscales) needs further study.

4.4 Predictive variables for parenting stress in parents of children who were surgically treated

Post-surgical seizure status was associated with a decrease of parenting stress. This association was, again, significant for the subscale Role Restriction. The child's becoming and remaining seizure free is accompanied by less seizure-related parental uncertainty and decreasing caretaking intensity, which together appear to afford more freedom of movement to both the child and the parent.

Intelligence was associated with stress scores on Mood and inversely associated with stress scores on Distractibility/Hyperactivity, both subscales of the Child domain. One may conjecture that children who function on higher cognitive levels are more aware of the impact that epilepsy has on their life, which affects their mood negatively. It is also conceivable that these children can organize their hyperactivity better into goal-directed activities whereas the hyperactivity of lower functioning children is more stress provoking for the parent because of its random nature. Clearly, more research is needed to test these assumptions.

4.5 Strengths and limitations

We measured parenting stress shortly before epilepsy surgery in the child, hence in a very stressful but also hopeful period of the parents' lives. Furthermore, only seven of the items of the PSI (spread over 4 subscales) could reasonably be interpreted as immediately related to the imminent surgery (blind evaluated by OB and AJS). In future research, one may measure the amount of parenting stress that is more directly related to the illness condition of the child, e.g., by including the Pediatric Inventory for Parents (PIP).[28]

We asked parents of healthy control children to participate because our main purpose was to control for re-test effects. We did not opt for a group of children with a different chronic illness and/or a different (or no) surgical intervention, because the comparison with those groups would entail illness-specific sets of unwished for influencing variables. As the groups differed in intelligence, the question arose whether higher stress in parents of patients than in control parents was due to epilepsy or IQ. Parenting stress decreased in parents of patients after epilepsy surgery, whereas there were no significant changes in IQ in these patients. This led us to conclude that parenting stress is for a large part directly related to the epilepsy. Tapering off anti-epileptic medication can have effect on the parents' perception of their child's medical condition. Parents can feel either relieved because the seizures have disappeared and no longer need pharmacological treatment, or worried because the seizures may recur during or after drug reduction. Unfortunately, in this study the effect of anti-epileptic medication could not be investigated because of the wide variation in type, dosage and number of antiepileptic drugs.

The small size of the group did not allow analyzing variables such as etiology, type of epilepsy and of surgery. However, for the present study, stress-relevant consequences of these variables, such as intelligence and seizure severity, were considered as of more importance.

4.6 Clinical implications

The increased parenting stress in parents of patients with pharmacologically intractable epilepsy calls for counseling with respect to coping with the intricacies of childhood epilepsy.[29] In the period surrounding epilepsy surgery, counseling should help to install realistic expectations with respect to not only the epilepsy outcome in terms of seizures but, as importantly, to mental development and psychosocial functioning, which even in the case of seizure improvement tend to remain impaired after epilepsy surgery.[30,31] Lower stress in parents will decrease stress in family functioning, improve quality of life of the children[32] and may decrease behavioral problems. The counseling can be procured by, e.g., epilepsy nurses or social workers, either or not through epilepsy patient societies.

Highlights

- Parenting a child with refractory epilepsy increases parenting stress.
- Parenting stress is still high two years after epilepsy surgery.
- Stress decreases most in parents of children with post-surgical seizure freedom.
- Parenting stress does, however, not normalize after epilepsy surgery.

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Appendix 5.1: Parenting Stress Index: two domains and 13 subscales with measurement pretension and interpretation of high scores

Parent domain – expresses the degree to which parent feels unfit for her/his parenting task, making her/him feel inadequate and tense

1. **Competence:** degree to which parent feels to be not sufficiently capable and skillful when relating to the child, often together with negative self-perception, low self-esteem, lack of confidence and locus of control external (pre-stage of depression)
2. **Role restriction:** degree to which parent feels her/his parenting role to trap her/his freedom and identity. High scoring parents feel dominated and controlled by the child's requirements and needs, often together with ambivalent feelings (both anger and guilt towards the child)
3. **Attachment:** degree to which parent feels affectively insufficiently tied to the child. High scoring parents feel unable to understand the child's feelings and they have a distanced, chilly parent-child relationship
4. **Depression:** degree of parent's discontent with respect to her-/himself and her/his life conditions. High scoring parents are incapable to mobilize physical and psychic energy; they lack assertiveness and feel unhappy, guilty and apathetic, frustrating their ability to act with authority and firmness towards the child
5. **Experienced health:** degree to which parent feels physically fit or plagued by ailments such as sleep problems and/or fatigue
6. **Social isolation:** degree to which parent feels lonely and isolated from friends, acquaintances and others who could offer emotional or material support
7. **Spouse:** degree to which parent feels dissatisfied by relationship with partner. High scoring parents experience a lack of practical and emotional support by partner. Spouses undertake few joint activities; they disagree on parenting and on interacting with child. Marker of marital conflicts, deficient marital solidarity and intimacy.

Child domain – expresses the contribution of particular child features (as felt by parent) to the parent's overall stress experience

8. **Adaptability:** degree to which parent experiences child as flexibly adapting to changes in her/his physical and social environment. High scoring parent experiences the child as a) nagging and unable to switch from one activity to another, b) avoiding strangers c) overreacting to changes in everyday family routines and d) once upset, difficult to calm down
9. **Mood:** parent's impression of the child's affect / temperament. High scoring parents experience the child as unhappy or depressed, varying a lot in affect, apathetic or aggressive and giving few signs of joy or happiness
10. **Distractibility/Hyperactivity:** high scoring parents experience their child as being overactive, restless, distracted, having a short attention span, having trouble sitting still and being incapable of finishing tasks
11. **Demandingness:** degree to which parents feel the child demanding their attention, for example by crying a lot, being clingy or constantly asking for help)
12. **Reinforces parent:** degree to which parent feels the child to give positive feedback on her/his behavior. High scoring parents experience themselves as to receive few positive signs from the child, a serious threat for the parent-child relationship
13. **Acceptability:** degree to which parent experiences the child as satisfying her/his expectations of physical, intellectual and emotional aspects of functioning. High scoring parents are dissatisfied

Chapter 6

Parents experience problems in psychological and family functioning two to four years after their child's epilepsy surgery

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Abstract

Objectives: To explore whether parents experience problems in their own psychological wellbeing and their family functioning two to four years after their child's epilepsy surgery and whether these problems are associated with epilepsy variables, demographic and cognitive variables and parent-observed behavior problems of the child.

Methods: Of the 65 approached families, parents of 31 children participated by completing the Brief Symptom Inventory, the Family Questionnaire and the Child Behavior Checklist. High scores indicating clinically relevant problems were reported and called 'problem scores'. Correlations between results of questionnaires and demographic and illness variables (abstracted from medical files) were computed for fathers and mothers separately. By comparing the group with at least one problem score with the group without problem scores, risk factors for parent-perceived problems in their own psychological functioning and in family functioning were explored.

Results: 30% of the mothers had problem scores on hostility and on communication within their family. Only a few fathers obtained problem scores, most of these pertaining to their family's organization. Not one parent had a problem score regarding their partner relationship. Many parents had problem scores on behavior problems in their child. Brain area of surgery was the only epilepsy variable related to parents' wellbeing and family functioning, with lowest problem scores for the hemispherotomy group. Scores on behavioral problems in the child were also lowest for children after hemispherotomy and for those who had achieved freedom of seizures and anti-epileptic drugs. Fathers of older children experienced more problems than those of young children.

Conclusions: Parent's wellbeing and family functioning cannot be understood from epilepsy or epilepsy surgery variables only, but are related to the child's age and behavior. Having epilepsy is associated with emotional and behavior problems and limits children in developing age-appropriate self-dependence. These problems are not resolved after achieving seizure freedom and have great influence on the family. Professionals should set realistic expectations of epilepsy surgery and should assess, acknowledge and follow up problems of parental psychological wellbeing and family functioning, regardless of the outcome.

1. Introduction

'I am supposed to be happy, but I am not. I am sad and confused and I feel guilty about not being able to be happy together with my family.' This is the reaction of a mother several months after successful epilepsy surgery in her youngest adolescent daughter. The mother had adapted her life to her daughter's epilepsy. She had developed a keen alertness to her daughter's precarious situation, constantly checking whether her child was all right and whether a seizure might be on the way. After five years of active epilepsy, epilepsy surgery stopped the seizures, but not the mother's over-alertness.

Parents of a child with epilepsy are at increased risk of psychological problems, such as depression, anxiety, and increased stress.[1-6] Furthermore, the child with epilepsy is at increased risk of behavior problems, anxiety, and depression.[7-10] Parental and child problems usually interact.[8,11]

Epilepsy surgery is a physically safe and efficient treatment for carefully selected patients with drug-resistant epilepsy.[12,13] However, the achievement of postoperative seizure freedom does not automatically resolve psycho-social problems that, prior to surgery, had developed in the child or his parents and, if any, siblings. Whereas changes in behavior and emotional wellbeing of children after epilepsy surgery have been reported,[14-16] studies addressing parental problems after epilepsy surgery are scarce. A qualitative study before and after pediatric hemispherotomy, revealed a positive change in the children's family situation after surgery.[17] Another study reported an improved health-related quality of life and emotional wellbeing of parents two years after epilepsy surgery in their child.[18] Additionally, we reported a decrease but not normalization of stress in parents after their child's epilepsy surgery.[4]

Knowledge about how parents fare after epilepsy surgery in their child is necessary for care professionals to provide adequate support for parents, enabling parents to provide a safe and stable base for their children. In the present study we explore parental perceptions of their own psychological wellbeing, their family's functioning, and their perceptions of their child's behavior, two to four years after their child's epilepsy surgery. We systematically studied relationships with demographic, cognitive, and illness variables.

2. Methods

Parents of all 65 children who had been treated with epilepsy surgery (callosotomies excluded) between June 2010 and June 2012 in the Wilhelmina Children's Hospital [University Medical Centre Utrecht (UMCU), The Netherlands] were approached by

phone to ask for their participation in this cross-sectional study. They were requested to complete three questionnaires addressing their perceptions of their own current psychological functioning, the functioning of their family, and their child's behavior. In addition, they reported on their paid working hours per week, their highest completed education,[19] and whether they had received psycho-social counseling (by a psychologist or social worker) since their child's epilepsy surgery. Data were gathered between September and December 2014.

The medical ethics review committee of the UMCU concluded that the Dutch law on Medical Research Involving Human Subjects did not apply to this study. However, to comply with good clinical practice we obtained informed consent from the 31 participating parents and children above the age of 12 years for completing the questionnaires for research purposes.

2.1 Instruments

2.1.1 The Brief Symptom Inventory (BSI)

The BSI[20] is a widely used self-report questionnaire addressing psychological problems in adults. The Dutch adaptation was used.[21] The BSI consists of 53 items organized into 9 problem dimensions: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. For descriptions of the dimensions see Appendix 6.1. Each item can be answered on a five-point scale, ranging from 0 = 'no problems at all' to 4 = 'extreme problems'. Raw scores are converted to seven-point population-normed scores ranging from 'very low' (normed score 1) to 'very high' (normed score 7) with mean score 4. High scores suggest more than normal psychological problems: normed scores 6 and 7, corresponding to the 80th and 95th percentile respectively, are clinically relevant.[20] Theoretical foundations, test reliability and validity are adequat.[21,22]

2.1.2 The Dutch Gezinsvragenlijst (GVL)

The Dutch GVL[23] is a questionnaire assessing family functioning as perceived by parents. The GVL is eligible for parents with children who have a (developmental) age of 4 years and above. The GVL assesses five basic dimensions of family functioning: Responsiveness, Communication, Organization, Partner Relation and Social Network. For descriptions of the dimensions see Appendix 2. Each item can be answered on a 5-point scale, ranging from 1 = 'totally disagree' to 5 = 'totally agree'. Raw scores are converted to population-normed deciles ranging from very low (decile 1) to very high (decile 10). High scores

refer to more than normal problems (e.g. lack of responsiveness, poor communication, disorganization, relational dissatisfaction and poor social network) in family functioning. Decile scores 9 and higher, corresponding to the 80th percentile and higher, are clinically relevant. Test reliability and validity are good.[23]

2.1.3 The Child Behavior Checklist (CBCL)

The CBCL[24,25] is, with its two versions (for children aged 1½–5 and for children aged 6–18 years), the most widely used questionnaire to evaluate parents' perceptions of their child's emotional and behavioral problems. Each of the items presents a description of a behavioral or emotional problem. Answers are marked on 3-point scales, ranging from 0 = 'not true' to 2 = 'very or often true'. Raw scores are converted to population-normed T-scores. T-scores above 60, corresponding to the 84th percentile and above, are clinically relevant.[24,25] Reliability and validity are adequate.[26]

Apart from the Total Problems scale (internalizing and externalizing together), both 'broad-band' scales are used in the present study. 'Internalizing problems' refers to maladaptive behavior directed at keeping emotions inside, such as anxious, depressed and withdrawn behavior. 'Externalizing problems' are maladaptive behaviors that are directed to the individual's environment, such as rule-breaking and aggressive behavior.

2.1.4 Data from the medical files

Cognitive functioning and illness variables of the children who had undergone epilepsy surgery were retrieved from medical files. Intelligence was assessed pre-surgically and 1 to 2 years post-surgically using the most suitable instrument per child (e.g., WISC-III, BSID-II). The Verbal Intelligence Quotient (VIQ), Performance IQ (PIQ) and Full Scale IQ (FSIQ), or for very young or developmentally delayed children the developmental index (DI) were used. We used the post-surgical data when available; for six children, only pre-surgical data were available. For the two children who scored below the lowest norm value, intelligence was estimated (100 * mental age / calendar age).

Analyzed epilepsy variables were: age at epilepsy onset, age at surgery, time between surgery and participation, brain area of surgery side of surgery, etiology, seizure freedom since surgery (no seizures between surgery and participation, except for acute postoperative seizures during the first month after surgery) and current anti-epileptic drugs (AEDs).

2.2 Data management and analyses

Statistical analysis was performed using IBM SPSS Statistics version 23.[27] Associations between questionnaire results and demographic and illness variables were computed for fathers and mothers separately.

Pearson's Product Moment Correlation was used for relating continuous variables to continuous or dichotomous variables and Spearman's Rank Test was used to relate ordinal to continuous variables. Correlations were considered strong between 0.5 to 1.0, moderate between 0.3 to 0.5 and weak between 0.1 to 0.3.[28] When Spearman's Rank Test was not applicable we used eta, a measure that is suitable to investigate associations between categorical and continuous variables. Eta was considered large when > .51, moderate when between .36 and .51 and small when < .36.[28] For associations between categorical variables Cramer's V or Fisher's Exact Test was performed, with large effect sizes between 0.5 to 1.0, moderate between 0.3 to 0.5 and weak between 0.1 to 0.3.[28]

A one-way ANOVA was performed to investigate the relation between brain area of surgery and intelligence. We explored risk factors (demographic and illness variables) for problems in psychological wellbeing or family functioning by comparing the group of mothers having at least one problem score with the group of mothers without problem scores. The same procedure was followed for fathers. In both analyses we used Chi-square for categorical variables and Student's t-tests for continuous variables. When multiple risk factors were found, hierarchic logistic regression was performed to identify the strongest predictor. Assumptions for the statistical tests were met.

3. Results

3.1 Participants and non-participants

In spite of repeated attempts by phone and by mail, six of the 65 families could not be reached. Parents of ten families did not wish to participate and parents of 18 families agreed to participate but did not return the forms, despite repeated requests. In December 2014, data from 31 families had been collected. Because of the age ranges of the instruments, not all parents of the 31 families completed all questionnaires. In some cases, only the father or the mother participated.

Information from medical records of all 65 children was used to compare participants with non-participants (Table 6.1). The differences between the groups are only significant for brain area of surgery and etiology.

Table 6.1: Demographic and illness variables of children and work, education, and counseling variables of the participating parents

Children	Participants (n = 31)	Non-participants (n = 34)
Sex, number (%)		
Male	17 (55)	19 (56)
Female	14 (45)	15 (44)
Age, mean (sd; range) years	10.2 (5.5; 3–21)	10.6 (5.8; 3–21)
Age at surgery, mean (sd; range) years	7.3 (5.2; 0–18)	8.1 (5.6; 1–17)
Age at epilepsy onset, mean (sd; range) years	2.9 (3.6; 0–12)	3.6 (3.4; 0–13)
Epilepsy duration, mean (sd; range) years	4.8 (3.8; 0–16)	5.0 (3.8; 0–16)
Post-surgical interval, mean (sd; range) years	3.1 (0.6; 2.2–4.1)	3.3 (0.6; 2.2–4.2)
Brain area of surgery, number (%)		
1 = hemispherotomy	11 (36)*	5 (15)
2 = temporal	5 (16)*	18 (53)
3 = frontal	11 (36)	9 (26)
4 = other[a]	4 (13)	2 (6)
Side of focus/surgery, number (%)		
Right	16 (52)	13 (38)
Left	15 (48)	21 (62)
Etiology, number (%)		
1 = MCD	11 (36)	10 (29)
2 = HS	0 (0)*	6 (18)
3 = tumor (glioma, cavernoma, DNET)	7 (23)	12 (35)
4 = other[b]	13 (42)*	6 (18)
Seizure free, number (%)	18 (58)	22 (65)
AED free, number (%)	15 (48)	12 (35)
Most recent FSIQ, mean (sd; range)	60 (21.4; 30–116)	67 (27.1; 10–110)
VIQ, mean (sd; range)	63 (21.7; 30–115)	67 (26.4; 10–110)
PIQ, mean (sd; range)	61 (23.3; 30–113)	69 (28.4; 10–111)

Parents	Mothers n = 31	Fathers n = 31	
Level of education			
Low	6	8	NA
Middle	8	13	NA
High	17	10	NA
Have had counseling			
Yes	13	11	NA
No	18	20	NA
Work hours/week			
Mothers (n = 31), mean (sd; range)	17.0 (11.4; 0–32)		NA
Fathers (n = 31), mean (sd; range)	37.0 (15.0; 0–80)		NA

MCD = malformation of cortical development; HS = hippocampal sclerosis; DNET = dysembryoplastic neuro-epithelial tumor; AED = anti-epileptic drugs; FSIQ = full scale intelligence quotient; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; NA = not applicable.

[a] Central resection, occipital resection or posterior disconnection. [b] Stroke/hemorrhage, infarction/ischemia, traumatic injury, tuberous sclerosis complex, encephalopathy. * Chi-square $p < 0.05$.

3.2 Parents' perceptions of their psychological wellbeing, family functioning and child behavior

3.2.1 Self-perceived psychological wellbeing

Table 6.2 shows mean scores per dimension of the BSI and the proportions of parents with problem scores. Almost one third of the mothers scored high on hostility (30%).

Twelve mothers (40%) and four fathers (13%) scored high on at least one of the BSI dimensions. In two families both parents scored high on at least one of the dimensions.

Table 6.2: BSI mean standardized scores and proportion of high problem scores in mothers and fathers

	BSI mother (n = 30)				BSI father (n = 31)			
			Problem score: percentile > 80				Problem score: percentile > 80	
	Mean	sd	n	%	Mean	sd	n	%
Somatization	3.8	1.1	2	6.7	3.4	0.9	2	6.5
Obsessive-compulsive	3.5	1.5	4	13.3	3.5	0.9	2	6.5
Interpersonal sensitivity	4.7	0.8	4	13.3	4.2	0.6	1	3.2
Depression	3.7	1.1	4	13.3	3.3	0.9	1	3.2
Anxiety	3.8	1.2	5	16.7	4.2	0.6	1	3.2
Hostility	4.8	0.9	9	30.0	4.2	0.5	1	3.2
Phobic anxiety	5.3	0.6	6	20.0	5.1	0.4	2	6.5
Paranoid ideation	3.7	1.2	4	13.3	3.5	1.0	3	9.7
Psychoticism	4.3	0.6	2	6.7	4.3	0.7	3	9.7
Total	3.6	1.7	5	16.7	2.4	1.5	2	6.5

3.2.2 Parent-perceived family functioning

Five families could not complete the GVL because their children's calendar age or developmental age was too low. Mean decile scores and the proportions of parents with high scores on the GVL are presented per dimension in Table 6.3. Almost one third of the mothers had problem scores on Communication (30%) and a quarter of the fathers had problem scores on Organization (23%). None of the parents had problem scores on Partner relation.

Seven mothers (27%) and 10 fathers (38%) had problem scores high on at least one of the GVL dimensions. In four families both parents had problem scores on at least one dimension.

Table 6.3: GVL mean decile scores and proportions of high scores in mothers and fathers

	GVL mother (n = 26)				GVL father (n = 26)			
			Problem score: percentile > 80				Problem score: percentile > 80	
	Mean	sd	n	%	Mean	sd	n	%
Responsiveness	4.7	2.5	1	3.7	5.0	2.7	3	11.5
Communication	6.3	2.9	8	29.6	5.2	3.1	5	19.2
Organization	4.5	2.2	1	3.7	5.5	2.8	6	23.1
Partner relation	3.8	2.7	0	0.0	4.1	2.5	0	0.0
Social network	5.6	2.6	4	14.8	5.4	2.8	5	19.2
Total	4.7	2.7	3	11.1	4.5	2.8	3	11.5

3.2.3 Child behavior

Seven children could not be assessed with the CBCL due to having a higher age (n = 3) or lower developmental age (n = 4) than the age range of the instrument. In one case, the CBCL was not returned. Mean scores on Externalizing problems, Internalizing problems, and Total behavior problems are reported in Table 6.4, as well as the proportions of children with problem scores. Mothers and fathers reported more problem scores on Externalizing problems.

Forty-three percent of the mothers and 48% of the fathers had problem scores on at least one of the CBCL scales.

Table 6.4: CBCL T-scores and proportions of high scores

	CBCL mother (n = 23)				CBCL father (n = 21)			
	T-score		High score: percentile > 84		T-score		High score: percentile > 84	
	Mean	sd	n	%	Mean	sd	n	%
Internalizing problems	55.6	10.0	6	26.1	54.9	10.7	6	28.6
Externalizing problems	53.3	10.7	8	34.8	52.9	10.7	7	33.3
Total behavior problems	56.3	9.9	8	34.8	53.5	10.0	6	28.6

3.3 Correlations of BSI, GVL, and CBCL with demographic and illness variables

We calculated all associations between the normed scores on the questionnaires (BSI, GVL, and CBCL) and the demographic and illness variables (see online Supplementary Table 1 for the complete correlation table). Variables that had no strong correlations with

any dimension on the BSI, GVL or CBCL were: FSIQ, VIQ, PIQ, age, epilepsy onset age, epilepsy duration, operation side, operation age, etiology, interval between operation and participation, parents' working hours, parents' education, and parents' counseling. Table 6.5 summarizes all strong associations, defined as eta > .51 or Pearson correlation > .50. Correlations within and between the BSI and GVL are not reported, since they are inherently related. Cells show the specific dimension, the size of association, and for Pearson correlations the p-value.

Table 6.5 reveals the following relationships, reading from left to right, top to bottom:

Sex: Mothers of boys perceived themselves as more obsessive-compulsive than mothers of girls.

Brain area of surgery: Fathers of children who had undergone temporal surgery perceived themselves as more hostile than fathers of children who had surgery in other areas. Mothers' self-perceived problems in social networks increased from low to high with the type of surgical resection in their children: hemispherotomy, temporal, frontal and 'other' brain areas, respectively. Mothers' and fathers' reported internalizing behavior and mothers' reported total problem behavior of their child increased in that same order. Fathers' reported externalizing and total behavior problems of their children followed a slightly different order: from lowest for hemispherotomized children, to more problems in children with resection in frontal, temporal and 'other' brain areas, respectively.

Seizure and AED freedom: Mothers as well as fathers of seizure-free children reported lower scores on internalizing behavior than parents of children with less favorable seizure outcome. In addition, fathers of children who were free of AEDs reported lower scores on internalizing behavior than those of children who still used AEDs.

Child behavior: More externalizing behavior problems in their child reported by fathers was related to more self-perceived depression and hostility in mothers. More reported internalizing behavior problems by fathers and mothers was related to more self-reported social network problems and total problems in family functioning by mothers.

3.3.1 Exploration of complex associations

Brain area of surgery was associated with many domains of parental problems (see Table 6.5). Since we did not expect a direct relation between this variable and parental wellbeing, we analyzed whether child characteristics differed between the four surgery groups. The most prominent difference pertained to intelligence ($F = 4.37$; $p = .011$) with the lowest IQ in children who had undergone a hemispherotomy.

Parent-perceived internalizing behavior of the child appeared to be strongly associated with three illness variables: brain area of surgery, seizure freedom, and AED freedom (see Table 6.5). To check for interrelatedness we analyzed the associations between these three illness variables. Seizure freedom and AED freedom were strongly related (Fischer exact = 20.99; $p < .001$). Although not statistical significant, the association between brain area of surgery and seizure freedom was strong (Cramer's V = 0.501, $p = .051$): 10 out of the 11 hemispherotomy patients became seizure free, compared to 8 out of the 20 patients after temporal, frontal, or 'other' resections. The association between brain area of surgery and AED freedom was moderate and non-significant (Cramer's V = 0.390, $p = .194$).

3.4 Risk factors for problems in psychological and family functioning

To investigate which parents were at risk for problems in psychological or family functioning, we compared demographic and illness variables in the group of mothers who had at least one problem score on the BSI or GVL, with those of mothers who had no problem scores. The same analysis was performed for fathers. Mothers with (n = 14, 45%) and those without (n = 17) problem scores could not be distinguished on any of the variables. However, fathers with problem scores on at least one dimension (n = 12, 39%) did significantly differ from those without (n = 19). Children of fathers with problem scores were older ($t = -2.42$; $p = .022$), had a higher age at surgery ($t = -2.33$; $p = .027$), and had had epilepsy for a longer time ($t = -2.33$; $p = .027$). A multivariate analysis (hierarchic logistic regression) with these three age-related variables revealed that current age of the child was the strongest predictor for having at least one high score. Mean age of children of fathers with one or more high scores was 13.0 years (sd = 5.3) and of children of fathers without high scores 8.4 years (sd = 5.0).

4. Discussion

4.1 Main findings

Two to four years after epilepsy surgery in their child, almost one-third of the mothers perceived themselves as hostile and a similar proportion reported communication problems within their family. Overall, few fathers perceived problems concerning their psychological wellbeing or family functioning. The dimension on which fathers reported most problems pertained to the organization of their family life. Interestingly, none of the parents perceived problems in their spousal relationship. Many parents reported behavior

Table 6.5: Strong associations with between parents' psychological problems, family functioning, child behavior, and illness and demographic variables

	Psychological problems (BSI) Mothers' self-perception	Psychological problems (BSI) Fathers' self-perception	Family functioning (GVL) Mothers' perception	Family functioning (GVL) Fathers' perception	Child behavior (CBCL) Mothers' perception	Child behavior (CBCL) Fathers' perception
Sex of the child	Obsessive-Compulsive (Pearson r = 0.666; p < .000)					
Brain area of surgery		Hostility (eta = 0.566)	Social Network (eta = 0.547)		Internalizing (eta = 0.562) Total (eta = 0.545)	Internalizing (eta = 0.686) Externalizing (eta = 0.561) Total (eta = 0.679)
Seizure freedom					Internalizing (Pearson r = -0.535; p = .008)	Internalizing (Pearson r = -0.710; p < .001)
AED freedom						Internalizing (Pearson r = 0.510; p = .018)
CBCL Internalizing behavior problems Mothers' perception			Social Network (Pearson r = .568; p = .011) Total (Pearsons r = .567; p = .011)			
CBCL Externalizing behavior problems Mothers' perception						

CBCL Total behavior problems Mothers' perception			
CBCL Internalizing behavior problems Fathers' perception		Social Network (Pearson r = .623; p = .006) Total (Pearson r = .588; p = .010)	
CBCL Externalizing behavior problems Fathers' perception	Depression (Pearson r = .502; p = .020) Hostility (Pearson r = .529; p = .014)		
CBCL Total behavior problems Fathers' perception			

problems in their child. Brain area of surgery was the only illness variable related to aspects of parents' wellbeing (fathers' self-perceived hostility) or family functioning (mothers'self-perceived social network), with least problems reported in the hemispherotomy group, and most in the group of surgeries in 'other' brain areas. Parent-reported child behavior problems were also least in the hemispherotomy group. Children who were free of seizures and AEDs had less behavior problems than children with ongoing seizures and AED use. Fathers of older children experienced more psychological and family problems than those of young children.

4.2 Parental psychological wellbeing and family functioning

With two exceptions, all mothers had less paid working hours than their partners. This may explain why mothers reported more psychological problems than fathers: as primary caregivers they were confronted more often with their child's difficult situation. This has been suggested previously,[5,29] but research including paternal primary caregivers is scarce.[30]

Parental hostility and problems in family communication both relate to anger and conflict in interaction (see Appendices 6.1 & 6.2). The reason for increased anger and conflict in mothers after their child's epilepsy surgery remains to be elucidated. At least part of the self-perceived hostility in mothers was related to father-reported externalizing behavior problems of the child. Maybe, in families where there are struggles between mother and child after epilepsy surgery, the mother explains these by her own hostility and the father by the child's negative behavior. Other factors could also explain mothers' anger and conflict, such as unmet expectations, losing her role as an essential care-giver, and having to find a new life purpose.

That fathers of adolescent children experience more problems compared to fathers of young children might be explained by their need for better organization within the family. This is supported by the moderate but significant correlation between children's age and fathers' score on organization (online Supplementary Table 1). Children with epilepsy are continuously supervised, which may result in restricted development of age-appropriate autonomy, self-dependence, and responsibility taking. These deficits show themselves during adolescence and have an impact on family organization.[31] The relation of these problems with age is supported by our previous finding that parents of older children reported more parenting stress after their child's epilepsy surgery than parents of younger children.[4]

None of the parents reported problems in their partner relationship. This is in line with our earlier finding that spouse-related stress was increased before epilepsy surgery

but decreased to normal levels two years after surgery.[4] Maybe, when the relationship survives the stress of having a child with refractory epilepsy, it remains shock proof after epilepsy surgery.

Unexpectedly, most illness variables, such as seizure freedom and ages at epilepsy onset and at surgery were not related to parent-perceived psychological and family functioning. Early epilepsy onset is often related to more severe epilepsy syndromes and lower cognitive functioning, which may have a negative impact on parents' wellbeing.[32] Seizure freedom would mean that parents no longer have to deal with the restrictions[25,33] and anxiety[3,5,6] caused by unexpected seizures, which may positively influence parent-perceived psychological and family functioning. However, the improved medical situation of their child also allows parents to process the impact of their child's illness, which may induce psychological stress. Adapting to a new situation has its own challenges which may explain why parents still experience psychological problems, regardless of their child being free of seizures and medication. For patients themselves, this process has been described as the 'burden of normality'.[34,35] Apparently, this notion is not only applicable to patients, but also to people in their social environment. The mother cited in the introduction, who could not feel happy after her daughter's successful epilepsy surgery, is a moving example.

The only epilepsy-related variable that was associated with parent-reported wellbeing and family function was brain area of surgery, with least problems in parents of children who underwent hemispherotomy. This relation may be mediated by the children's behavior problems, which were less in children with hemispherotomies compared to temporal, frontal, and 'other' surgeries.

The problems that parents encounter after their child underwent epilepsy surgery are not population-specific. Parents of children with AED-treated epilepsy are also at increased risk of psychological problems, such as depression, anxiety and high stress levels.[1-3,5,6] For chronically ill children in general, a review on parenting concluded that parenting stress was greater in caregivers of children with a chronic illness compared to caregivers of healthy children.[36] The major difference, however, is that epilepsy surgery often cures the illness, but still the parents experience problems.

4.3 Parents' view on their children's behavior

Many parents reported internalizing as well as externalizing behavior problems in their child. Internalizing behavior was less problematic in seizure-free or AED-free children than in children with recurrent seizures or those still on drugs. Conceivably, children who

attain seizure freedom may feel less anxious, have less somatic complaints and tend to withdraw less in social contacts and activities than when they had ongoing seizures.[10] Freedom of anti-epileptic drug use is inseparable from seizure freedom and can be felt as an extra insurance that the epilepsy is cured. The relationship between withdrawal of AEDs and decrease of behavior problems may also be mediated by the clearing away of negative side effects that some AEDs can have on behavior.[37]

Behavioral problems were related to brain area of surgery. The relatively large proportion of children who became seizure-free after hemispherotomy may explain the low level of behavior problems in this group. Furthermore, children with hemispherotomies had the lowest intelligence levels. Intellectual disability may impact not only parental expectations but also how children live up to these expectations. This is corroborated by our previous study in another epilepsy surgery cohort in which we found that parents of children with low IQ experienced less stress related to their child's mood than parents of children with higher IQ.[4]

4.4 Limitations

Two inevitable aspects of doing research with parents of children who had epilepsy surgery as participants, are the heterogeneity and small size of the population.

Our study may have inclusion bias since only half of the approached families participated. Parents experiencing problems may have thought that participation was important or, contrarily, may not have been motivated to participate. Furthermore, participants and non-participants differed on relevant epilepsy variables such as brain area of surgery and etiology, with more children after hemispherotomy and less after temporal resection in the participants group than in the non-participants group. This renders our sample less representative for the epilepsy surgery population.

Having access to only post-operative data on parents' perceptions of their wellbeing, family functioning and their child's behavior, we were not able to evaluate the effect of surgery by comparing these to the pre-operative situation.

4.5 Conclusion

Two to four years after epilepsy surgery in their child, many parents report more than normal problems in psychological or family functioning.

Parents' wellbeing and family functioning are related to age and behavior problems of the child, rather than to epilepsy or epilepsy surgery variables. The necessity of continual

guardianship to warrant their safety restricts children with epilepsy in developing age-appropriate self-dependence. Self-dependence is limited as well by cognitive problems in some of them. Epilepsy surgery does not resolve these behavior problems that have great influence on the family.

4.6 Clinical implications

Prior to epilepsy surgery it is important that care providers not only attend to the child with epilepsy, but apply a family-centered approach in which realistic expectations of surgical treatment are fostered. After successful epilepsy surgery, parents and children may experience difficulties in their psychosocial wellbeing which should be assessed, acknowledged and treated when required.

Highlights

- We studied parents' wellbeing and family problems after their child's epilepsy surgery.
- Some parents report problems in self-perceived psychological or family functioning.
- Perceived problems are related to age and behavior problems of their child.
- Child and parent problems to some degree remain after epilepsy surgery.
- The wellbeing of all family members of a child after epilepsy surgery should be considered.

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Appendix 6.1: Brief Symptom Inventory: interpretation of high scores per dimension

Brief Symptom Inventory
1. Somatization (SOM): physical complaints, nausea, pain, dizziness, probably as a result of anxiety and panic.
2. Obsessive-Compulsive (OC): repetitive thoughts and compulsive acting, concentration problems, difficulty with remembering and decision making.
3. Interpersonal Sensitivity (IS): shyness, self-conscious, feelings of inferiority, failure and fear of being criticized. Social anxiety and possibly social phobia.
4. Depression (DEP): suicidal thoughts, lonely, gloomy, feeling worthless and helpless.
5. Anxiety (ANX): feeling nervous, scared, tense, and restless. Experiencing panic and trembling.
6. Hostility (HOS): feeling irritable and angry and quarrelling frequently.
7. Phobic Anxiety (PHOB): phobic anxiety, specific fears like agoraphobia, fear of traveling, crowds, or activities.
8. Paranoid Ideation (PAR): suspiciousness, hostility, megalomania, possible personality disorder.
9. Psychoticism (PSY): withdrawn life style, feeling lonely in presence of company, worrying about psychological health and being sinful.

Appendix 6.2: Family questionnaire (the Dutch Gezinsvragenlijst): explanation of the dimensions

GVL
1. Responsiveness (RES): the sensitivity of parents to the needs of their child. Emotional (hugging), cognitive (giving advice), and social (complimenting). Sensitive parents often react adequately. Responsive parents accept their child, have concern for their child, reassure and support their child, and offer their child security.
2. Communication (COM): the way parents address their child. Understanding and trusting their child, listening to their child, communicating empathically and without conflict.
3. Organization (ORG): how the family life is arranged and structured. Do all members have and honor their own tasks, is there a clear routine, are there open relations between family members, and how does the family deal with problems.
4. Partner Relation (PR): the quality of the relationship between the parents. Conflicts and fighting between parents.
5. Social Network (SN): the whole of the family's social relations: neighbors, friends, relatives.

Part III

Overview

Chapter 7

Social functioning in children after epilepsy surgery: a literature review

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Abstract

This first review on social functioning of children after epilepsy surgery provides an overview of the literature between 2003 and 2019. Twenty-four papers, drawn from PubMed and the reference lists, met the inclusion criteria. The papers addressed two categories of social functioning: social cognition (n = 4) and general social functioning (n = 20). Overall, studies that compared with healthy peers revealed children who had undergone epilepsy surgery to have more problems in both social cognition and general social functioning. Only half of the studies found some improvement in social functioning in the first year(s) after epilepsy surgery, but this only pertained to general social functioning, not to social cognition. Potential explanations for the persistence of the problems in social *cognition* are possibly related to the critical period of brain maturation, lacking improvement of impairments in related cognitive domains and a defective underlying brain condition – rather than the epilepsy. Problems in general social *functioning* may be explained by the adjustments the children and their families had to make due to the epilepsy, which are only partially undone after epilepsy surgery. Restrictions in daily and social activities and behavioral patterns are intertwined, leading to deficiencies in the development of social skills. The neurological and behavioral explanations are likely to be interrelated in light of the multifaceted and complex nature of social functioning. Epilepsy surgery is a successful treatment of seizures for carefully selected patients, but it does not appear to solve the problems in social functioning associated with having had chronic epilepsy. As social functioning is an important aspect of healthy development, it should be attended to during the treatment of children with epilepsy and when counseling patients and families about recovery after epilepsy surgery.

1. Introduction

Epilepsy is the most common chronic neurological disorder in children. It is strongly associated with neuropsychological problems[1] and has a great impact on the child's social functioning.[2-5] Epilepsy surgery is recognised as the most effective way to treat focal lesional epilepsy, when anti-epileptic drugs (AEDs) fail to control seizures.[5] Successful epilepsy surgery is largely defined in terms of seizure freedom. Having seizures, using AEDs, and the stigma of being a person with epilepsy negatively influence social functioning,[2,6] as could the radical change that epilepsy surgery can bring to the lives of these children and their families. Therefore, it is important to consider children's social functioning before and after epilepsy surgery.

In our search for literature on social functioning after epilepsy surgery, we came across two different paradigms. One focusses on social cognition as a neuropsychological concept and uses psychological tests to asses this functionality, whilst the other considers general social functioning to be an aspect of daily functioning that can be assessed with questionnaires and interviews of both the child and important others. Social cognition is an umbrella term for the cognitive and emotional processes required to interpret the behaviour and internal states of others and to respond in an appropriate manner.[7] Human social cognition – usually studied in terms of Theory of Mind (ToM) – is the ability to make inferences about other people's minds.[8] This capacity to attribute mental states – like thoughts, emotions and intentions – to others is considered essential for interpreting and predicting other people's behaviour.[9] An important component of ToM is the capacity to derive from another person's facial expression how she or he is feeling. More generally, in order to understand another person's mental state and behaviour, you must be able to recognise subtle nonverbal signals, such as the emotion displayed in the facial expression of other persons.[10,11] At another level, general social functioning can be described as daily social functioning, and includes the quality of their social life, participating in social activities, social competence, and establishing and maintaining social relations.

Social cognition and general social functioning are mutually dependent and children with epilepsy (CwE) are at risk for impairments in both.[12] Deficits in social cognition have an impact on general social functioning, like engaging in social interactions in a manner consistent with age-appropriate expectations.[3] And vice versa, a lack in social activities may hamper the ability to develop social cognition.

We aimed to provide an overview the existing literature on social functioning in children whose epilepsy had been treated surgically. We included studies from both paradigms, focussing on social cognition as a neuropsychological concept and general social functioning as an aspect of daily functioning.

2. Methods

The PubMed database was searched (last search at December 27th 2018) for relevant research articles, using the search terms: [epilepsy surgery] AND [(child*) OR (pediatric)] AND [(social) OR (social cognition) OR (emotion recogn*) OR (theory of mind)].

Inclusion criteria for the review of papers examining social functioning of children after (and preferably also before) epilepsy surgery were: (1) reporting on social functioning in children (0-18 years; in studies also including adults, the data on children had to be separately reported or retrievable), (2) a sample size of at least 10 children, (3) at least one assessment after epilepsy surgery, (4) results should pertain to at least one measured dimension (scale) of a test/questionnaire addressing social functioning, social behaviour perceived by relevant others or social cognition, (5) original research, written in English and, (6) published between 2003 and 2019. Initial selection of studies, based on title and abstract, was done by CM and OB independently. Final selection of studies based on full texts, and extraction of data were also done by CM and OB. The reference lists of the included articles were searched to identify further studies that met the inclusion criteria.

3. Results

The search resulted in 263 hits, of which 20 met the inclusion criteria. Three papers were added as a result of screening the references of these 20 papers. One not yet published (but accepted) article of our own group was included, resulting in 24 papers. Four papers reported on social cognition assessed by specific social-cognitive tasks (Table 7.1) and 20 papers reported on general social functioning assessed by questionnaires, observational screening, or interviews (Table 7.2).

3.1 Social cognition

Only four papers reported on social cognition (before and) after epilepsy surgery in children (Table 7.2).

Comparing pre- with postsurgical data

Of the two papers in which pre- with postsurgical data were compared, one reported no change in social cognition,[13] and the other described a gradual improvement in social cognition, but only in children older than 12 years. The improvement was, however, not different from the increase seen in controls.[11]

Comparing surgical with non-surgical CwE

One study included non-surgical CwE and found no difference between the surgically treated children and non-surgical CwE in recognizing emotions.[14]

Comparing (surgical) patients with healthy peers

All four papers compared patients with healthy peers and reported poorer social cognition in patients than in controls.[11,13-15]

Relation with seizure freedom

In neither of the two papers that included seizure freedom in the analyses, a relation between seizure status and social cognition was found.[11,13]

Other variables related to social cognition

All four papers described the outcome of analyzing relations between social cognition and demographic and/or illness variables (other than seizure status). One paper reported no relation with epilepsy variables, but a temporary decline in children aged < 12 years and not in older children.[11] Later epilepsy onset was found to be associated with better social cognition in three papers.[13-15] Two papers reported children with a temporal origin of epilepsy to have better social cognition than children with extra-temporal[13] or fronto-central[14] epilepsy. One paper reported children in whom the amygdala was resected to have worse on ToM than children in whom the amygdala was not included in the resection.[132]

3.2 General social functioning

Twenty papers reported on general social functioning after epilepsy surgery in children (Table 7.1). Among these, 13 provided data that could be compared to the norm; the overall outcome was that general social functioning is impaired in these children.[16-22,24,25,29,31,32,34]

Comparing pre- with postsurgical data

In 15 papers, pre- and post-surgical data were compared. Eight papers reported positive changes in social functioning after surgery.[12,16,17,21,22,32-34] Based on observations or child reports, these positive changes included reduced social anxiety[16] and social inadequacy,[17] increased social competence and social activities,[34] and improved social skills[32] and social interaction.[21] Parents reported decreased emotional and behavioral difficulties,[22] increased social activity,[12,33,34] and increased social maturity.[32] The remaining papers reported no change after surgery with respect to psychosocial functioning,[18] social competence,[19] socialization,[29] social problems,[20,25,31] and social QoL.[30]

Table 7.1: Social cognition after epilepsy surgery in children

Study	Sample	Design	Age at surgery (years): mean (range)	Post-surgery follow-up range (yrs)	Seizure outcome Seizure Free (SF) or Engel class I–IV	Domain(s) measured	Measures	Outcome
Braams et al.* 2019,[13] not yet published	Surgical patients (N = 15), healthy peers (N = 30)	Longitudinal: before surgery, and at least 2 of 3 follow-up assessments after surgery	7.1 (4–11)	0.5–2	SF: 13 (87%) after 2 years	Theory of mind (ToM)	ToM Storybooks	No change in ToM after surgery. Higher VIQ, later onset of epilepsy and temporal origin were associated with better ToM. Children in whom the amygdala was resected performed worse on ToM. Seizure freedom was not related to ToM.
Braams et al.,* 2015[11]	Cross-sectional: Surgical patients (N = 41), healthy peers (N = 82). Longitudinal: Surgical patients (N = 11); healthy peers (N = 22)	Cross-sectional: post-surgery; longitudinal: before surgery, and 3 follow-up assessments after surgery	Cross-sectional group: N/A, age at 2-year follow-up assessment: 13.5 (4.2–20) Longitudinal subset: 11.9 (6.5–17.2)	0.5–2	N/A	Facial emotion recognition	Facial Expression of Emotion: Stimuli and Tests (FEEST)	Surgically treated children were poorer at recognizing emotions than controls. Younger children (< 12y) had a decline after surgery, but had recovered to presurgical level after 2 years. Adolescents had a continued increase in performance after surgery. Neither seizure freedom, nor any other epilepsy variable was related to facial emotion recognition.

Golouboff et al., 2008[14]	CwE (N = 37; of whom 21 treated surgically), healthy peers (N = 37)	Cross-sectional: CwE (considered as one group, regardless of whether they were surgically treated or not) vs. controls	N/A; age at assessment: 13.2 (8–16)	N/A	N/A	Facial emotion recognition	Facial emotion recognition test for children: Test de Reconnaissance des Expression Faciales pour Enfants (TREFE)	CwE performed worse than controls, there was no difference between CwE with and without surgical treatment. Early-onset and temporal localization were related to more impaired recognition of facial expressions of emotion.
Pinabiaux et al., 2013[15]	Surgical patients (N = 25); healthy peers (N = 50)	Cross-sectional; post-surgery only	9.7 (4.1–18.1)	1–7.25	I: 25 (100%)	Memory for facial emotion recognition	Facial emotion recognition test for children (TREFE)	Healthy peers showed enhanced memory for happy and fearful faces; surgical group (temporal lobe epilepsy) showed enhanced memory for fearful faces only. There was an impact of early seizure onset on the identification of fearful faces.

* Studies have partially overlapping samples. CwE = children with epilepsy; N = number; VIQ = verbal intelligence quotient.

Table 7.2: General social functioning after epilepsy surgery in children

Study	Sample	Design	Age at surgery (yrs): mean (range)	Post-surgery follow-up range (yrs)	Seizure outcome: Seizure Free (SF) or Engel Class I–IV	Domain(s) measured	Measures	Outcome
Andresen et al., 2014[16]	Surgical patients (N = 100)	Longitudinal; before surgery and 1 follow-up assessment after surgery	10.8 (N/A)	Range N/A; mean = 0.7(sd = 1.1)	I 84 (84%) II 5 (5%) III 4 (4%) IV 7 (7%)	Psychosocial functioning, social anxiety	CBCL parent report; Revised Children's Manifest Anxiety Scale (RCMAS) self-report	No difference between pre- and post-surgical parent-reported social problems. Children with left frontal (not those with temporal) lobe epilepsy had higher levels of pre-surgical social anxiety, that reduced significantly after surgery.
Braams et al., 2017[17]	Surgical patients (N = 23); healthy peers (N = 39)	Cross-sectional: CwE vs. healthy peers; Longitudinal: before surgery, and 3 follow-up assessments after surgery	12.8 (N/A)	0.5–2 year	SF: 17 (74%) after 2 years	Personality	Dutch Personality Questionnaire self-report	Before epilepsy surgery, CwE considered themselves more (socially) inadequate, perseverant and recalcitrant than healthy peers. Social inadequacy decreased after surgery. There was no relation between seizure freedom and personality traits. Sporadic relations were found with gender, lobe of surgery and use of levetiracetam.

Conway et al., 2018[12]	Surgical patients (N = 111)	Longitudinal: before surgery and one follow-up assessment after surgery	12 (N/A)	1	SF: 79 (71%)	Social domain QoL	QoLCE parent-report	Higher QoL scores in domain 'social activity' after surgery compared to baseline. Patients who were seizure free had significantly more increase in social QoL than those with recurrent seizures.
Danielsson et al., 2009[18]	Surgical patients (N = 24)	Longitudinal; before surgery and 1 follow-up assessment after surgery	12.6 (4.2–19.4)	2	I: 7 (29%) II: 7 (29%) III: 5 (21%) IV: 5 (21%)	Psychosocial functioning	Children's Global Assessment Scale (CGAS); examiner report	After surgery, scores on psychosocial functioning had changed positively in 10 children, not changed in 6 children, and changed negatively in 8 children. Of all 7 seizure free children, none changed negatively.
Dwivedi et al., 2017[19]	Surgical patients (N = 57), non-surgical CwE (N = 59)	Longitudinal: before surgery and 1 year follow-up assessment after surgery	Surgical group: 9 (0.8–17); non-surgical group: 10 (2–17)	1	Surgical group SF: 44 (77%); Non-surgical group SF: 4 (7%)	Social competence	Vineland Social Maturity Scale parent report	No significant change after 1 year in social competence for both groups. No significant difference between both groups. (But significant between-group change favorable for the surgical group.)
Elliot et al., 2008[20]	Surgical patients (N = 20); non-surgical CwE (N = 12)	Longitudinal: before surgery (or baseline), and 2 follow-up assessments after surgery/ baseline	14.2 (8.5–18.3)	1–2	SF: 10 (50%) after 2 years	Psychosocial functioning	CBCL parent report	Between-group difference over time was significant: surgical group had a reduction in social problems over time, whereas they increased in the non-surgical group. Seizure freedom and lower number of AED's were predictors of improved social function.

Table 7.2 continues on next page.

Table 7.2: ***Continued***

Study	Sample	Design	Age at surgery (yrs): mean (range)	Post-surgery follow-up range (yrs)	Seizure outcome: Seizure Free (SF) or Engel Class I–IV	Domain(s) measured	Measures	Outcome
Gröppel et al., 2018[21]	Surgical patients (N = 20)	Non-statistical Longitudinal: before surgery, and 2 follow-up assessments after surgery	1.3 (0.3–2.7)	0.3–2	IA: 13 (65%) I: 1 (5%) III: 1 (5%) IV: 5 (25%)	Social Interaction Quotient (SIQ)	Denver Scales	Group-wise (infants and toddlers together): median pre-operative SIQ = 59 and median 2 years post-operative SIQ = 72. Pre-operative SIQ was higher in the infant compared to the toddler group (64 vs 56). Post-operative, in seizure- and AED free children, SIQ was higher in infants compared to toddlers (86 vs 63).
Hannan et al., 2009[22]	Surgical patients (N = 13)	Longitudinal: before surgery and at least 2 follow-up assessments after surgery	10.8 (5–17)	0.4–8.5	IA & II: 10 (77%) IV: 3 (23%)	Emotions, behavior, and psychosocial impairment	Strengths and difficulties questionnaire (SDQ) parent report	Overall difficulties gradually decreased over 3 follow-ups. Authors suggest, but did not analyze, that improvement was related to seizure freedom.

Hum et al., 2010[23]	Surgical patients (N = 27)	Qualitative; post-surgery only	N/A. Age at interview: 16.5 (11.3–21.2)	1.5–3.4	IA: 13 (48%) I: 2 (7%) II: 3 (11%) III: 4 (15%) IV: 5 (19%)	Self-perception of social functioning	Semi-structured, open-ended interview on physical, psychological, social, and cognitive/ academic experiences	Many of the seizure free participants reported more independence, increased confidence, and improvement in their social experiences. Nevertheless, most participants, irrespective of seizure status, continued to report problems with peer relations and isolation.
Korneluk et al., 2003[24]	Surgical patients (N = 13)	Cross-sectional: post-surgery	11 (14-17)	1.6–2	I: 10 (77%) II: 2 (15%) III: 1 (8%)	Psychosocial functioning	CBCL parent report and teacher report form (TRF)	Parents reported higher scores on social problems compared to the normative sample, but teachers did not. No difference was found between children with (n=9) and without (n=4) removal of the amygdala.
Law et al., 2015[25]	Surgical patients (N = 147), non-surgical CwE (N- = 40)	Longitudinal: before surgery (or baseline) 1 follow-up assessment 1 year after surgery/baseline	12.2 (3.1–18.3)	0.4–4.1	surgical group SF: 95 (65%). non-surgical group SF: 8 (20%)	Psychosocial functioning	CBCL parent report	No difference in social problems between baseline and follow-up for both groups. Data from baseline and follow-up pooled showed more social problems in the nonsurgical group relative to the surgical group. Seizure freedom was not related to social problems, but early onset of epilepsy and number of used AEDs were. Low VIQ and PIQ were related to poorer social functioning.

Table 7.2 continues on next page.

Table 7.2: ***Continued***

Study	Sample	Design	Age at surgery (yrs): mean (range)	Post-surgery follow-up range (yrs)	Seizure outcome: Seizure Free (SF) or Engel Class I–IV	Domain(s) measured	Measures	Outcome
Mikati et al.* 2008[26]	Surgical patients (N =17), non-surgical CwE (N = 12)	Cross-sectional: post-surgery	11.2 (4–16)	Range N/A; mean = 2.4 (sd = 0.25)	I: 14 (82%) II: 2 (12%) III: 1 (6%)	Social domain QoL	QoLCE parent report	No difference in social QoL between the surgical and non-surgical group.
Mikati et al.* 2010[27]	Surgical patients (N = 19), non-surgical CwE (N = 19), healthy peers (N = 19)	Cross-sectional: post-surgery	7.7 (2–14)	Range N/A; mean = 3.8 (sd = 2.3)	I: 15 (79%) II: 1 (5%) III: 2 (11%) IV: 1 (5%)	Social domain QoL	QoLCE parent report	No difference in social QoL between the three groups when analyzed together. Analyzed per two groups (three combinations possible) showed a difference only between the non-surgical group and healthy peers.
Puka and Smith, 2015[28]	Surgical patients (N = 71), non-surgical CwE (N = 38)	Cross-sectional; post-surgery	13.2 (4.3–18.9)	4–11	surgical group SF: 40 (56%) in last year. non-surgical group SF: 16 (42%).	Social functioning	QoL in Epilepsy for Adolescents self-report; QoLCE parent report	No significant difference in social QoL between the surgical and non-surgical group. Seizure free patients had better social QoL, irrespective of having had surgery. AED use was negatively associated with social functioning.

Pulsifer et al., 2004[29]	Hemispherectomy patients only (N = 71)	Longitudinal: before surgery (in 53 patients) and 1 follow-up assessment after surgery	7.2	Range N/A; mean = 5.4	I: 46 (65%) II: 16 (23%) III: 6 (9%) IV: 3 (4%)	Socialization development/ adaptation	Developmental Profile (DP II) parent report	There was no difference in socialization DQ between before and after hemispherectomy for all three etiology groups. At follow-up, socialization DQ was significantly lower for children with dysplasia, compared to Rasmussen's encephalitis and vascular etiology.
Sabaz et al., 2006[30]	Surgical patients (N = 35)	Longitudinal: before surgery and 1 follow-up assessments after surgery	11.9	1–1.5	SF: 20 (57%)	Social domain QoL	QoLCE parent report	There was no significant difference in social QoL between pre- and postoperative scores; seizure free patients showed significant improvements in social interactions and activities.
Smith et al., 2004[31]	Surgical patients (N = 30); non-surgical CwE (N = 21)	Longitudinal: before surgery (or baseline) 1 follow-up assessment after surgery/ baseline	13.3 (6–18)	1	I: 17 (57%) II: 5 (17%) III: 2 (7%) IV: 6 (20%)	Psychosocial functioning	CBCL parent report; Piers-Harris (PH) Children's Self-Concept Scale self-report	No difference between surgical and non-surgical patients: no change after surgery in both groups. Seizure status did not predict psychosocial scores or change. Improvement in social subscale was largest in those with more social problems before surgery. Seizure outcome and temporal vs extra-temporal localization were not significantly associated with change of psychosocial outcome variables. Self-concept improved more in older children compared to young children.

Table 7.2 continues on next page.

Table 7.2: ***Continued***

Study	Sample	Design	Age at surgery (yrs): mean (range)	Post-surgery follow-up range (yrs)	Seizure outcome: Seizure Free (SF) or Engel Class I–IV	Domain(s) measured	Measures	Outcome
Thomas et al., 2010[32]	Surgical patients (N = 16)	Longitudinal : before surgery and up to 3 annual follow-up assessments after surgery	6.6 (0.7–13.3)	1–3	I: 15 (94%) II: 1 (6%)	Social competence; social age	VSMS parent report; Gesell's Developmental Schedule/Binet-Kamat Scale of Intelligence child assessed by psychologist	VSMS score and personal social skills significantly improved 3 years after surgery. Older seizure onset age and shorter duration of seizures prior to surgery were related to more social age gain at follow-up.
Titus et al., 2013[33]	Surgical patients (N = 28)	Longitudinal: before surgery, and 1 follow-up assessment after surgery	12.7 (8–16)	0.5–1.2	I: 15 (54%) II: 6 (21%) III: 4 (14%) IV: 3 (11%)	Social domain QoL	QoLCE parent report	Significant increase of social activities subscale – however, due to an increase in engagement in social activities rather than social interaction. Improvement of seizure status was related to improvement in socialization.
van Empelen et al., 2005[34]	Surgical patients (N = 21)	Longitudinal: before surgery, and at least 2 follow-up assessments after surgery	11.2 (6.2–16.8)	0.5–2	I: 15 (71%) II: 4 (19%) III: 2 (10%)	Health related QoL and self-perceived competence	HAY (How Are You) questionnaire, child and parent version; Harter Self-Perception Profile for Children/ Adolescents	Improvement of social activity after surgery was reported by children and parents. Increase in self-perceived social competence and self-worth after surgery.

* Studies have partially overlapping samples. N = number; CBCL = Child Behavioural Checklist; QoL: Quality of life; QoLCE = Quality of life in childhood epilepsy questionnaire; CwE = children with epilepsy; AED = anti-epileptic drugs; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; VSMS = Vineland Social Maturity Scale; sd = standard deviation.

Comparing surgical patients with non-surgical CwE

Seven papers reported on the comparison of general social functioning between surgical patients and non-surgical CwE. In four papers, no difference between the two groups emerged: three papers reported no difference in social QoL between post-surgical children and non-surgical CwE[26-28] and one found no difference in change of social problems between the two groups.[31] One study found more social problems in the non-surgical group compared to the surgical group, when pre- and postoperative data were pooled.[25] In two studies, changes over time in social competence and social behavior differed between the groups, in favor of the surgically treated group.[19,20]

Comparing surgical patients with healthy peers

Two studies included a control group of healthy peers. Before epilepsy surgery, CwE considered themselves as more inadequate, socially inadequate, perseverant, and recalcitrant than did their healthy peers.[17] Mikati et al. (2010) found no difference in social QoL comparing patients four years after surgery with healthy peers.[27]

Relation with seizure freedom

Eleven studies evaluated the relation between general social functioning and whether or not achieving seizure-freedom after surgery. Two studies qualitatively described a positive relation. In one study, authors stated that in none of the seven seizure-free children psychosocial functioning had changed negatively (compared to a negative change being observed in 6 of the 17 children with recurrent seizures).[18] In the other study, many of the seizure-free participants reported greater independence, increased confidence, and improvement in their social experiences.[23]

Four studies reported a statistically significant relation between seizure freedom and more increase in social QoL,[12] better social QoL,[28] and improvement of social functioning after surgery[20,30] compared to those who had not achieved seizure-freedom. In one study, not seizure freedom per se, but improvement of seizure status was related to improvement of socialization.[33]

In four studies seizure-freedom was not related to social domains of personality,[17] social problems,[25] social QoL,[27] or changes in social behavior and self-concept.[31]

Other variables related to general social functioning

Ten studies analyzed relations between social functioning and demographic and/or illness variables other than seizure status. Earlier age at onset was related to poorer social functioning in two studies,[25,32] as was longer duration of epilepsy.[32] One qualitative study

reported better post-operative social interaction in children operated upon during infancy (< 1 year) compared to toddlers (between 1 and 3 years of age), but only in children who were seizure- and AED free.[21] Three studies found a negative effect of higher numbers of AED's used[20,25,28] and one of levetiracetam use specifically.[17] Of the four studies that analyzed the relation between surgical area and social functioning, two found an effect. In one study, children with left frontal (but not those with right-sided or temporal) epilepsy had higher level of pre-surgical social anxiety, which reduced significantly after surgery.[16] In the other study, social inadequacy was less in children with temporal compared to extra-temporal epilepsy and surgery.[17] In the other two papers, the analyses yielded no significant relations with area (temporal vs extra-temporal),[31] or with removal of the amygdala or not.[24] In the study on children before and after hemispherotomy, socialization DQ was significantly lower in children with cortical dysplasia, compared to children with Rasmussen's encephalitis and with vascular etiologies.[29] One study found low – compared to normal – VIQ and PIQ to be related to poorer social functioning.[25] Self-concept improved more in older children than in young children[31] and when comparing boys and girls, boys rated themselves as more recalcitrant.[17]

Relation with duration of follow-up

Duration of follow-up differed between the papers from several months up to 11 years. Most studies (n = 15) had follow-up intervals of between 1 and 3 years after surgery. In only five studies, the follow-up interval was longer than three years.[22,25,27,28,29] Two of these, with follow-up ranges between 0.5 and 4.1 years[24] and between 4 and 11 years,[28] analyzed the relation between follow-up interval and change in social functioning. Neither found a relation between duration of follow-up and change in social functioning. Scrutinizing the other 18 papers, we found no indication that positivity or negativity of the results varied with duration of follow-up. Five papers suggested in their discussion section that longer follow-up could possibly have revealed more positive change,[16,17,19,20,23] and two papers stated that one year[32] or even only 6 months[34] should be enough to disclose positive change.

4. Discussion

In this literature review of social functioning in children (before and) after epilepsy surgery, two main topics imposed themselves: social cognition, as a neuropsychological concept and general social functioning, as an aspect of daily functioning. The literature was scarce and no study evaluated both aspects of social functioning simultaneously. Of the studies that compared post-surgical with pre-surgical data, approximately half concluded to (some) improvement in general social functioning, but evident improvements of social

cognition were not reported. Comparing surgical patients with non-surgical CwE, the majority of studies found no difference in either general social functioning or social cognition. Only one study reported more social problems in the non-surgical group relative to the surgical group. In two studies, the change over time differed between groups in favor of the surgical group, due to an increase of problems in social competence and social behavior in non-surgical CwE and a decrease of problems in the surgical group. In all but one study, surgical patients had poorer scores on social functioning than their healthy peers. Seizure freedom and lower numbers of AED's used, were in some studies related to better general social functioning, but not to social cognition. Later onset and temporal origin of epilepsy were associated with better general social functioning and social cognition in a few studies.

4.1 Social cognition

The only two papers on longitudinal studies of social cognition both described no relevant change after epilepsy surgery.[11,13] The first paper reports on ToM and the other on facial emotion recognition. In this second paper, however, there was an influence of age suggested: only the older children (13–17 years) gradually improved after surgery, similar to controls. The younger children (< 12 years) displayed a temporary dip in facial emotion recognition six months after surgery.[11]

There are a number of potential explanations for poor social cognition and for the fact that it fails to improve after epilepsy surgery. It should be noted that the explanations probably interact since the causes of affected social functioning in children with refractory epilepsy are complex, multifactorial, and interdependent.[35,36]

4.1.1 Disrupted cognitive development during critical periods of maturation

If the development of a cognitive function is hampered by abnormal neural activity during a critical period of brain maturation, it is unlikely that this cognitive function will ever develop fully later in life. An association has been demonstrated between an earlier onset of epilepsy and more severe social cognitive impairments.[37] Three studies on social cognition in this review confirmed that relation.[13-15] In the remaining study, the influence of epilepsy onset was not analyzed, but a relation was found between social cognition and epilepsy duration (interval between epilepsy onset age and surgery).[11] Abnormal brain activity during critical periods of development can disrupt the neural circuits responsible for various cognitive functions, including those implicated in social development.[38] Outside these periods, further development of this function is limited, if not impossible,[39] also when epilepsy surgery is successful, and seizure activity has stopped.

4.1.2 Persistent impairments in related cognitive domains

The lack of improvement in social cognition may be caused by persistent impairments in cognitive domains that are related to ToM abilities.[40-42] Children with epilepsy, particularly refractory epilepsy, are not only impaired in social cognition, but in a wide range of other cognitive functions such as attention, memory, intelligence, language, and communication.[43,44] These cognitive functions have also been found to improve slightly at most after epilepsy surgery.[45,46] None of the four studies on social cognition in this review, however correlated social cognition to other cognitive functions. Only broad measures such as IQ or VIQ, if any, were included to control for general cognitive functioning. The issue whether poor social cognition is part of an overall impairment of cognitive functioning, or rather a specific vulnerability in children before and after epilepsy surgery, remains to be tackled.

4.1.3 Complex relationship between seizures and cognition

The main goal of epilepsy surgery is to stop seizures. The formerly widely held assumption that cognition – social or otherwise – will improve as a result of the elimination of seizures implied the notion of a causal relation between seizures and cognition. Recent years have witnessed a shift in perspective, away from this 'epilepsy-centric' view.[35] Rather than seizures causing cognitive impaiments, , both seizures and cognitive impairments may co-occur as dual symptoms of an underlying condition. This view is supported by studies that fail to pinpoint a relation between seizure frequency and the severity of impairments in cognitive functions such as ToM.[39,47] Additionally, cognitive and behavioral problems have been observed in children with new-onset epilepsy, demonstrating that deficits are present in the very early stages of the disorder, before multiple seizures have had the opportunity to cause harm.[43,44] Thus, when cognitive impairments are not caused by seizures, but co-occur with seizures caused by an underlying etiology, cessation of these seizures is unlikely to improve (social) cognition. An exception may be children who suffer from so-called epileptic encephalopathy, in which the seizures contribute to aggravation of cognitive disturbances, more than can be expected on the basis of the underlying epileptogenic disorder alone.[48] There are no studies on social cognition available to confirm this; children who are candidates for hemispherotomy are mostly very young which complicates performing standard social cognition assessments.

4.2 General social functioning

Although positive changes in general social functioning were reported in about half of the longitudinal studies, clinically meaningful improvements were sporadic and sometimes unclear. For example, the post-surgical increase in social activities found in one study

turned out to be based on the ability to engage in activities, rather than by an increase in social interaction with peers.[33] In addition, self-perceived increase of social functioning after surgery was supported by the responses of only a few children, whereas the majority reported continued isolation and peer rejection after surgery.[23] In a study on personality, only one of the more negative personality traits that distinguished CwE from healthy peers, i.e., social inadequacy, improved significantly after epilepsy surgery.[17]

Explanations for a lack of improvement in general social functioning after pediatric epilepsy surgery in many studies, may involve factors related to the practical and psychological difficulties that may follow surgery, rather than to the medical consequences of epilepsy and the surgery. Epilepsy, particularly refractory epilepsy, is a severely debilitating disorder, and requires patients and their families to live restricted lives. Seizure freedom therefore marks a huge change in the daily lives of the former epileptic patient and calls for often drastic readjustments which may require significant time to be implemented.[49] This is in line with what was described in some of the included studies on general social functioning. Even when epilepsy surgery is successful, behaviors that have become entrenched in the habits of the child and her/his environment over the course of development may be difficult to overcome once the child is seizure free.[20] The current available literature does not suggest that longer follow-up periods would entail more positive change in social functioning compared to shorter follow-up, which underscores that problems in social functioning persist after epilepsy surgery.

Many children with epilepsy grow up with a feeling of being different or misunderstood, and such feelings may not disappear spontaneously after surgery.[23] Also, growing up under continuous supervision hampers children to develop self-dependence. Furthermore, deprivation from social situations due to seizures, fatigue, hospital visits etcetera, may lead to decreased social learning opportunities, which could lead to underdeveloped social cognition and social skills. In addition, the child's social environment may not change in response to her/his changed health condition after epilepsy surgery.[20] In one of the included studies it was noted that, although the children's perceptions of themselves and their own social ability changed after surgery, the negative attitudes of their peers towards them did not necessarily change, the remaining stigma hampering their integration. Seizure free children evaluated persistent stigma as the greatest barrier to improve social functioning. One child who had become seizure free after surgery and had changed school, reported no problems making friends, suggesting that a change in environment may be a protective factor in the child's reintegration and adjustment after surgery.[23]

The 'burden of normality' has previously been introduced to explain the difficulty of adjusting to the expectations that come with newly found health. Growing up as a

chronically ill child, needing and receiving extra care and protection may make the child feel insecure and dependent. Abandoning this illness role, accepting more responsibilities, and abandoning dependence may therefore be challenging for the child.[49] This 'burden of normality' may also apply to parents who had adjusted to having a sick child. They had provided continuous surveillance and concern, left their jobs, put their social lives on hold, and even disregarded their own health. All of these factors change once the child is no longer in constant danger of having seizures.[50] Fear of fits, persistent over-protection and continuously treating the child as though she/he were ill can strongly hinder the child's social readjustment after surgery.[7,49]

4.3 Limitations

The literature search provided only four papers on social cognition in children (before and) after epilepsy surgery. Only two of these, with partially overlapping sample of patients, had a longitudinal design. Given the importance of social cognition for everyday functioning and psychosocial development, the dearth of research on the effects of surgery is surprising and contrasts to the large amounts of research on other functional domains, such as intelligence, language and memory.[51,52]

One explanation for the scarcity of research on social cognition could be that social cognition is often considered a field separate from neurocognition (like language, memory and attention)[53] not being the primary focus of neuropsychologists. Another explanation, could be that social cognition is more difficult to assess through cognitive tests than other domains. Language and memory for example, are skills that can be learned (and tested) from texts, lists, and books. Social skills are, per definition, learned and practiced in social contexts, and therefore more difficult to operationalize with tests in an ecologically valid manner.

With a sample of 20 papers, general social functioning, evaluated through questionnaires, interviews, and observational screening was more frequently the topic of studies in children before and after epilepsy surgery than social cognition. However, the variety of instruments used between the studies was very wide. Also, the methods were rather indirect, relying largely on informants in the social environment of the child such as parents and teachers, or on the children's reflection on their own social functioning. In one study, parents of children with epilepsy reported social problems, but their teachers did not. The teachers, however, reported more severe signs of anxiety and depression.[23] These conflicting reports from parents and teachers render interpreting the results difficult. Perhaps the children behave differently at school and at home. A disadvantage of the

current self-report questionnaires could be that reflecting on one's social functioning relies on the insight that children have into their own behavior, which may be specifically unreliable in children with deficits in ToM.

4.4 Suggestions for further research

Longitudinal studies using standardized neuropsychological assessments including cognitive functions that are related to social cognition are required to examine the development of social cognitive functioning before and after epilepsy surgery in children. These should be combined with repeated evaluations of general social functioning, in order to disentangle the causes of poor social functioning in children with refractory epilepsy and search for changeable factors that could improve social functioning.

5. Conclusion

This literature review on social functioning in children (before and) after epilepsy surgery yielded a sample of studies that could be divided into two paradigms of social functioning: (1) social cognition as a neuropsychological concept, and (2) general social functioning as an aspect of daily functioning. Children with refractory epilepsy are at risk for problems in both, and these problems do not improve in a clinically meaningful way after epilepsy surgery. Rather, the scarce improvements are small and are overshadowed by remaining difficulties of social functioning. Potential explanations for lack of improvement in social cognition are related to the critical period of maturation, lack of improvement of other, related cognitive impairments and the underlying brain condition rather than to the seizures. That problems in general social functioning are persistent may be explained by the adjustments the children and their families had to make to living with epilepsy, which cannot be undone after epilepsy surgery. Restrictions and behaviors are entrenched and deficiencies occurred in the development of social skills. These explanations are likely to be interrelated in light of the multifaceted and complex nature of social functioning.

Epilepsy surgery is a successful treatment of seizures for carefully selected patients, but it does not solve the problems in social functioning associated with having refractory epilepsy. Given their importance for optimal development social cognition and general social functioning should be recognized as important aspects and addressed longitudinally during the treatment of children with epilepsy and their recovery after epilepsy surgery.

Highlights

- Social cognition and general social functioning are at risk in children with epilepsy.
- Epilepsy surgery does not solve the problems in social functioning in children.
- Epilepsy variables related to social functioning in children are sporadically found.
- Social functioning should be assessed before and after epilepsy surgery in children.

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Chapter 8

Summary and discussion

Social matters! Social functioning is a crucial part of life that is present from the very beginning. Hearing soothing voices, making eye contact, smiling, playing, learning by imitating, sharing, helping or being helped, relationships, working together, all depend on social interactions. Social functioning is at risk in people with a chronic illness and especially in children with medically difficult to treat epilepsy. Seizures, the need to take medication, restrictions in everyday activities, fatigue, hospital visits and the stigma of having epilepsy are just a few consequences of refractory epilepsy that can deprive children from age-appropriate social activities and interactions. This does not only affect the quality of life of these children and their family directly, but also limits the development of social skills through diminished experience.

Epilepsy surgery could form an extra threat to social functioning, since the majority of resections include brain structures and networks that are involved in social cognition.[1,2] On the other hand, when it leads to the expected seizure freedom or seizure reduction, epilepsy surgery can decrease the negative consequences of having epilepsy on general social functioning and increase quality of life. This thesis addresses social cognition in children before and after epilepsy surgery and other social 'matters', such as personality, general social functioning of these children, parenting stress, parents' psychological wellbeing, and the family's functioning as perceived by the parents. Social cognition is an essential part of general social functioning. It can be considered a specific neuropsychological function domain and will sometimes be discussed as such separately from general social functioning.

Summary of findings

In **part I**, '**Children**', it becomes clear that children with refractory epilepsy perform worse than healthy peers on tasks that assess recognition of emotions expressed by faces (chapter 2) and theory of mind (chapter 3). Both findings could not be explained solely by the lower intelligence of children with epilepsy than of the controls. Except for a transient decrease in recognizing emotions expressed by faces, that was seen in only the small sub-group of young children (aged < 12 years), epilepsy surgery had no effect on social cognitive functions. Two years after epilepsy surgery, children did not perform worse than the pre-surgically, but development of social cognition had not caught up with that of healthy peers either. In the patients, explorative analyses yielded little consistent correlations of social cognition with demographic and epilepsy variables. Only longer duration and earlier onset of epilepsy were found to be related to worse social cognition in the two studies (chapter 2 and 3). In the study described in chapter 3, we found that

children in whom the amygdala was resected had lower scores on tests of theory of mind (ToM) than children whose amygdala was not included in the surgical resection. In chapter 2, a relation with the amygdala could not be supported.

Based on our assessment of self-perceived personality, children with refractory epilepsy had higher scores on the personality dimensions of inadequacy (having vague anxieties, low self-confidence, and often depressed mood), perseverance (endurance, diligence, being dutiful), social inadequacy (being inhibited, shy and awkward in social contacts, and having difficulty to connect), and recalcitrance (an oppositional attitude towards others) when compared to healthy control children (chapter 4). After surgery, only social inadequacy diminished gradually. No convincing correlations between demographic or epilepsy variables and personality traits could be found.

In the literature review on social functioning in children before and after epilepsy surgery (**Part III**, '**Overview**', chapter 7), we found that the studies belonged to two different paradigms: 'social cognition' (a neuropsychological concept that is assessed by tasks) and 'general social functioning' (an aspect of daily functioning assessed by questioning the child itself, but mostly by collecting evaluations from informants in the social environment of the child, e.g. parents, teachers or peers. The findings underscore the risk of problems in social cognition for children with refractory epilepsy and confirm the lack of improvement after epilepsy surgery. Children who undergo epilepsy surgery are also at risk of developing problems in general social functioning, such as social anxiety, social isolation, and difficulties in social interactions. Some of the problems as reported by the children or the informants decreased after epilepsy surgery, but the majority of children continued to experience problems in general social functioning.

In **part II**, '**Parents**', we describe that parenting stress in parents of children with refractory epilepsy is more severe than that in parents of healthy control children, on all scales within the so-called *child domain* of the used stress questionnaire (the child domain distinguishes the sub-scales Adaptability, Mood, Distractibility/Hyperactivity, Demandingness, Reinforces Parent and Acceptability) (chapter 5). In the *parent domain*, stress was higher on three of seven subscales (Role Restriction, Health and Spouse). These findings reflect that parents' self-perceived stress was mainly related to specific features of the child. Although parenting stress decreased after epilepsy surgery, the change over time was not different from that reported by parents of healthy control children. Moreover, stress ratings remained high in parents of patients when compared to the population norm. Decrease of stress was most pronounced in parents of children who became seizure free and more prominent in subscales of the parent-domain than of the child-domain.

Two to four years after epilepsy surgery in their child, parents reported problems in their psychological and family functioning (chapter 6). Mothers reported problems on hostility (feeling irritable and angry and quarrelling frequently) and on communication within their family (being unsatisfied with the way they understand and trust their child, listen to them and communicating empathically and without conflict). Only a few fathers obtained problem scores, most of these pertaining to their family's organization (being unsatisfied with how the family life is arranged and structured, for example with respect to tasks and routine, and how the family deals with issues). These problems could, again, not be traced back to epilepsy variables of the child. Rather, the child's age and behavior were associated with parents' evaluations of their own psychological wellbeing and their family's functioning. Behavioral problems are common in children with severe epilepsy,[3-5] have a great impact on the family and parents' wellbeing and are usually not resolved by epilepsy surgery.

Taken together, there are problems in social development of children with refractory epilepsy and in social functioning of their parents, both before and after epilepsy surgery. Epilepsy surgery does not cause additional deficits in social cognition, but it does not improve scores on most of the used measures of social cognition and functioning either. Adverse personality traits and problems in general social functioning of the children as well as parenting stress of the parents decrease to some degree after epilepsy surgery, but remain problematic. Three years after epilepsy surgery in their child, parents experience problems in their psychological wellbeing and family functioning. Epilepsy-related characteristics were scarcely found to correlate with social matters.

Discussion

Relation between social cognition and epilepsy variables

In both our studies on social cognition in children before and after epilepsy surgery (chapters 2 & 3), we found a relation with onset age or duration of epilepsy. Children who had epilepsy for a longer time or who had an earlier onset age of epilepsy performed worse on social cognition tasks. This was also found in the only two other published studies on social cognition after epilepsy surgery in children.[6,7] Even in children with epilepsy who function at an average general cognitive level, Theory of Mind (ToM) was also found to be at risk and related to onset age of epilepsy.[8,9] It can be argued that epilepsy affects the neural circuitry that underlies social cognition, including the amygdala.[10] If early onset implicates more or earlier brain damage, patients with early-onset epilepsy are at an increased risk of affected neural networks and brain areas involved in social cognition

from the beginning, which has an ongoing negative effect during development. It could also be that the effect of early onset age on social cognition is not specific, but co-occurs with other cognitive impairments in children with epilepsy. Early onset age has often been supposed as to be relate to a general impairment of cognitive functioning,[11,12] and also to impairments of specific cognitive domains that are related to ToM abilities,[13] such as executive functioning[14] and language.[15] However, there is some evidence from our own studies (chapters 2 and 3), as well as from others,[8,9] that impairments in social cognition in children with epilepsy are not explained by lower intelligence (usually taken as an index of general cognitive functioning). Since we only used broad measures for general cognitive functioning and did not include results of specific cognitive domains, the specificity or generality of the impairment in social cognition of children before and after epilepsy surgery remains to be established. A retrospective analysis of two other tasks — memory for faces and memory for abstract line drawings (chapter 2) – using the same model as for recognizing emotion expressed by faces, showed no difference between patients and healthy peers. Although this analysis in a small subgroup is too weak to fare on, these results suggest that poor social cognition should not be fully attributed to an impairment of general cognitive functioning, and encourage further research.

Children in whom the amygdala was resected, regardless of the lateralization of the resected amygdala, had lower scores on tests of ToM than children whose amygdala was not included in the surgical resection (chapter 3). This difference in ToM existed already before surgery, which suggests that the epileptogenic zone had already comprised the amygdala. In our study on facial emotion recognition, however, we did not find a relation with the status of the amygdala. It could be that the tasks used in both studies, recognizing facial expressions of emotions (chapter 2) versus ToM (chapter 3), differ in their sensitivity to amygdala dysfunction. A large difference between the tasks is that in recognizing facial expressions, the emotion was presented and only needed labeling, whilst in ToM tasks children are required to reason on emotional situations and produce the emotional states themselves. The difference between findings may also be explained by a higher mean age (13.5 versus 7.1) – or maybe more importantly a higher mean onset age of epilepsy (5.9 versus 3.8) – of the children in the study on facial expressions of emotions, compared to the children who were included in the ToM study. This would be in agreement with the suggestion by Shaw et al., that damage to the amygdala only impairs ToM when it is acquired in childhood and not in adulthood.16 However, very little is known about the development of 'the social brain' and the specific role of the amygdala in children.[17]

Epilepsy surgery does not negatively affect social cognition, nor does it have a positive influence. We did not find correlations between social cognition measures and seizure

freedom (chapter 2 & 3). The unexpected finding that eliminating seizures did not improve social cognition suggests that seizures per se are not the cause of difficulties in social cognition, but rather co-exist with social cognitive impairments as a symptom of the underlying epileptogenic condition. This idea is supported by studies in which no relations were found between seizure frequency and the severity of impairments in ToM[18,19] and by studies in which cognitive and behavioral problems were found in children with new-onset epilepsy, thus in children who did not have many seizures to impact their development yet.[20,21] It should be noted that there is a subgroup of patients who suffer from so-called epileptic encephalopathy, in which the seizures and frequent EEG discharges are known to contribute to an aggravation of cognitive disturbances.[22] Since these children are mostly too young to be assessed with social cognition tasks, we cannot report results of this particular subgroup.

An explanation for the lack of improvement in social cognition after successful epilepsy surgery may be found in the so-called critical periods of brain maturation. In critical periods cognitive functions develop intensely. The development of social cognition may be disrupted by epilepsy during these periods, so that after surgery and after closure of these periods, further development is limited, if not impossible.[18]

To better understand the neurobiological substrate of social cognition impairments in children before and after epilepsy surgery, it would be interesting to compare our findings with those from studies on social cognition in children with other chronic (non-neurological) illnesses, preferably before and after a curative medical intervention. Unfortunately, we could not find studies investigating this. Social cognition in children was almost solely researched in populations with other neurological conditions (for example cerebral palsy and traumatic brain injury) or related to psychiatric features (for example autism, schizophrenia, or depression). There is some literature available on children with a heart condition, but neurological causes could not be ruled out – and were even suggested – as possible explanation for impaired social cognition in these children.[23,24]

Relation between general social functioning and epilepsy variables

Our literature review on general social functioning in children before and after epilepsy surgery (chapter 7) contains studies in which some relations with epilepsy variables were found, but also studies in which these were not found. For example, in four studies seizure freedom was correlated to better social functioning and in three studies earlier onset age or shorter duration of epilepsy was related to better social functioning (chapter 7). Neither seizure freedom nor epilepsy duration were related to personality traits of

children before and after epilepsy surgery (chapter 4). It is possible that problems in general social functioning are (partly) caused by impairments in social cognition and thus, to some extent, can be indirectly understood from neurobiological influences as discussed before. We think however, that problems in general social functioning can be better understood in light of a broader perspective, which will be discussed in the next paragraph.

Biopsychosocial model

Improvement of the medical situation, becoming seizure free, and lowering AED use appears to have limited positive impact on social matters in children who have undergone epilepsy surgery. This asks for a broader approach to explain the problems in social matters. We propose to interpret our findings in light of the biopsychosocial model (Figure 8.1). George Engel introduced this model in 1977 to give room to the social, psychological, and behavioral dimensions of illnesses, besides the biomedical dimension.[25] It helps to understand people's mental health. How patients feel is not only defined by their biological, medical condition, but also largely depends on psychological aspects such as coping strategies, intelligence, feelings of self-worthiness, and on their social context, including their family and friends. The model has evolved into a holistic model of illness and is increasingly used by medical specialties, particularly in the context of patient-centered care.[26]

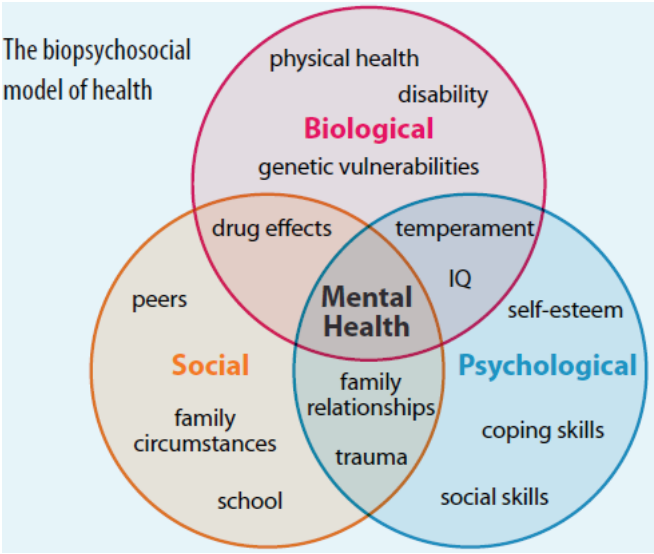

Figure 8.1: Diagram of the Biopsychosocial model.
Source: Psychology Today.

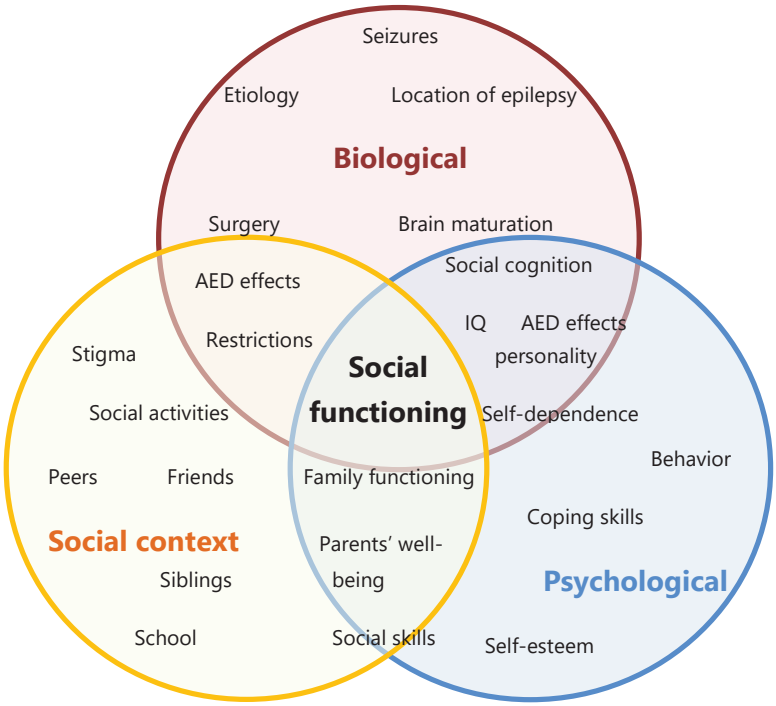

Figure 8.2: Biopsychosocial model on social functioning in children after epilepsy surgery.

In children before and after epilepsy surgery, the three dimensions – biological variables, psychological aspects, social context – interact and overlap. Figure 8.2 is an example of applying the biopsychosocial model on social functioning in children with epilepsy. The locations of the terms in the circles are not fixed but susceptible to interpretation. Aside from the medical aspects, children with epilepsy have to deal with stigma and restrictions.[27,28] They are at increased risk of behavioral problems, anxiety, and depression.[29-32] These, and more psychological and social features interact with the medical condition and together determine the child's social functioning.

The chronicity of refractory epilepsy causes these influences to interact for a long period, forming stable patterns that cannot be assumed to resolve instantly after successful surgery. Children with severe epilepsy grow up under constant supervision hampering them in the development of self-dependence. Curing epilepsy ends the seizure-related need for supervision, but does not make up for the insufficiently developed skills of independent functioning. Deprivation from social situations due to seizures, fatigue, hospital visits and other factors, lead to decreased social learning opportunities, which

may lead to underdeveloped social cognition, social skills, and could decrease self-worth. Being the center of attention, children with severe epilepsy are at risk of unintentionally becoming selfish and less able to be considerate to others, which can all the more become a problem once the epilepsy is cured.

Chronic refractory epilepsy has a large impact on the lives of the parents as well. Parents are at increased risk of psychological problems, such as depression, anxiety, and stress.[33-35] In our own studies, we found increased parenting stress (chapter 5) and problems in parents' well-being and family functioning (chapter 6), even until years after their child's epilepsy surgery. Parents reported highest stress in feeling restricted in their role as a parent and feeling socially isolated. This can be understood from the necessity of continual guardianship that parents have to provide to their child in order to warrant his or her safety, which changes their lives. Working less, feeling less freedom to go out, not being able to enlarge the freedom of their child are examples of adjustments parents have to make. Once the epilepsy is cured, the child's appeal on the parents' protection decreases, but ingrained strategies are not undone automatically. Parents may feel superfluous and may struggle finding new purposes in daily life. On the other hand, the lack of age-appropriate self-dependence of the child continues to require the special support from parents, complicating the parents' feeling of ambiguity.

Logically, the biopsychosocial processes of both child and parents interact, making it harder still to find a new balance. The frequently found correlation between social functioning and early epilepsy onset may be understood from the fact that early onset implies early parental worries about the child, early adaptive interactions with the child, and early epilepsy-related restrictions imposed upon the child. The difficulty in adjusting to the new situation after surgery, discarding the roles associated with chronic epilepsy and learning to function as a healthy person, is also described as 'the burden of normality'.[36,37] An illustrative example of this struggle of child and parents, is the finding that 42% of children who are free not only of seizures but also of anti-epileptic drugs after epilepsy surgery, still live with restrictions.[38]

Methodological considerations

The population of children undergoing epilepsy surgery is small and very heterogeneous in terms of underlying etiology, age at onset, level of cognitive functioning, seizure frequency, side and site of surgery, and many other factors. These differences make it difficult to identify disease-related variables that are associated with social cognition and social functioning, or with functioning in any area for that matter. This problem is, however,

inherent in performing research on children before and after epilepsy surgery. Varying in age from 0–18 years, the population 'children' covers a wide span of development. The difference in social functioning, and also other cognitive domains, between a young baby and an 18-years old adolescent is enormous which requires a variety of instruments covering the different features and stages of social functioning. It would have been interesting and worth-wile to analyze combinations of results of different tasks or used instruments per child, for example performance on recognizing emotions expressed by faces and on theory of mind, or comparing personality of the children as reported by the parents with self-reports by the children. However, the overlap of age ranges between different instruments was insufficient and would have led to very small groups of children being assessed with the same combination of instruments, which would have rendered proper analysis unfeasible.

We strengthened our studies by using a longitudinal design with one baseline and three follow-up measurements, thereby increasing our number of data-points. We also included a control group of two age- and gender-matched healthy control children (with their parents) per patient. The healthy peers were assessed at the same time intervals as the patients, to control for (normal) development. However, it was not possible to include a group of children with refractory epilepsy who had identical characteristics, except for being operated upon, to those of the included patients who underwent surgery. In our tertiary referral center, children with epilepsy who are considered candidates for surgery participate in a thorough multidisciplinary pre-surgical evaluation program. Whether or not they are selected for surgery depends on the results of several ancillary investigations. When considered suitable, all children will undergo surgery, leaving no comparable control group. We did not opt to include a group of children with a different chronic illness and/or a different surgical intervention because the comparison with such groups would entail illness-specific sets of confounding variables. As our control group of healthy peers had a higher level of general cognitive functioning compared to the patients, we corrected for intelligence in our analyses. For future research, however, we would suggest including a large group of children with various chronic illnesses to unravel which biopsychosocial determinants influence social matters most.

Another challenge of the studies presented here was the methodological difficulty of investigating 'social cognition'. Children do not learn social cognition as systematically as they learn, for example, to read and write in school. Social cognition develops through watching and engaging in social activities. What is socially adequate behavior cannot be captured by one standard. Behavior that is appropriate in one situation can be inappropriate in another, like telling a joke. Social standards also differ between,

e.g., cultures, countries, families, peer groups, and schools. Those variations render standardizing levels of accomplishment for social cognition more difficult than for skills learned at school or neuropsychological psychological domains such as intelligence, memory, and language. Assessing social cognition is a second challenge.[39] In order to test reading one needs a text and to test memory one needs a set of items, which both are easy to provide in a neuropsychological test setting. Testing social cognition would require social situations. We used two tasks, recognizing emotions expressed on faces that are presented on a computer screen as black-and-white photographs which the child is allowed to inspect for three seconds (FEEST),[40] and reading books with social story-lines (ToM Storybooks).[41] Being only simulations of social situations and not actual social situations as they would be in real life, both tasks may have a rather weak ecological validity. Moreover, these tasks require other cognitive skills as well, such as visuo-spatial and verbal abilities, and they do not assess the effects of social cues that facilitate everyday social interactions, such as prosody or body language.[39] Ideally, social cognition should be evaluated by observing children in social interactions, but this is time consuming, expensive, and difficult to validate reliably. Instruments to assess social cognition in children are scarce and we chose the best options available. The only alternative for the ToM Storybooks is Steerneman & Meesters's ToM test-R.[42] The ToM Storybooks are more appealing for children, with colorful illustrations that are enlivened with, e.g., doors that open, and separate pictorial response cards that the child can select and place on the characters. Facial emotion recognition was best assessed by the FEEST, since it was suitable for children above age 12 and could be adapted (shortened) for administration in younger children, yielding a broad age range of children that could be assessed with similar tasks.[40] With colored photos of children's faces as stimuli, the subtest 'emotion recognition' from the NEPSY-II is since 2010 an attractive alternative for the FEEST, although it has a smaller age-range (5–12 years).[43]

We used clinical questionnaires to evaluate personality and behavior in children and parenting stress, psychological problems and family functioning in parents. A disadvantage of using self-report questionnaires to evaluate personality in children may be that self-reflecting on social functioning relies on the insight that children have into their own behavior, which may be unreliable particularly in children with deficits in ToM. On the other hand, self-report provides insight into the child's own view of her or his functioning, rather than their parents'. An advantage of using clinical instruments is that study results can be translated directly to clinical practice. Usually, research instruments are used because they are less time consuming for the informants and researcher. However, in our experience, clinical samples of children with severe conditions and their parents are willing to invest time in research projects.

Clinical implications

Social cognition is not yet part of standard neuropsychological assessment in epilepsy surgery centers in Europe.[44] Given its importance for social development, social cognition, but also general social functioning should to be assessed systematically and longitudinally and added to the standard neuropsychological evaluations before and after epilepsy surgery. A family-centered approach in which also parents and siblings are screened for problems in psycho-social well-being is highly recommended since epilepsy in a child affects the whole family.[45]

Despite the high success rate of epilepsy surgery in terms of seizure freedom, problems on social matters in the child and the family do not resolve within two years after the child's epilepsy surgery. This is probably partly due to the earlier mentioned chronicity of severe epilepsy, which causes adjustments and habits that become firmly persistent. The movement towards early selection of pediatric candidates for epilepsy surgery in order to optimize seizure and cognitive outcomes[46] may also be advantageous for minimizing epilepsy-caused problems in social matters.

Psycho-education must be provided before surgery, not only covering the possible changes, but also the possible lack of change. Our own results have already led to improvements in our pre-surgical trajectory by innovating the information for children and their family to better prepare them for the operation and the period thereafter. Recently, a nurse practitioner, specialized in pediatric epilepsy surgery, has been hired to prepare families for the upcoming stressful period and screen whether they are in need of any guidance by a social worker or psychologist. More attention is needed to guide families in the post-surgical period. After successful epilepsy surgery the positive (medical) consequences are gratefully and rightfully addressed, but there is a chance that families also experience disappointment due to ongoing problems in social functioning and that these are underestimated and unrecognized by care professionals. Through social media, we are in contact with parents of children with epilepsy surgery in their histories, in order to learn from their experiences and to find out what we can improve in the care for (future) families.

In my opinion, social cognition and social functioning are crucial to address, not only before and after epilepsy surgery of children, but of all families with a child who suffers from a chronic illness. We found only few illness-specific variables that were related to social matters. Other variables, such as intelligence, child behavior, and age, had stronger relations with social functioning and/or social cognition. Applying the biopsychosocial model, it is conceivable that illness variables are related to social matters indirectly, by

mediating or moderating other factors. Using the biopsychosocial model as a frame of reference helps understanding the difficulties that families with children with a chronic illness experience, and gives insight into which dimensions are susceptible for improvement. A nice pragmatic way to incorporate this broad view into the clinic and research is suggested by Rosenbaum and Gorter: use the 'F-words' in counseling children and their families: function, family, fitness, fun, friends, and future.[47] My personal interest would concern the development of self-dependence and autonomy in chronically ill children. My hypothesis is that this development is strongly related to coping strategies. Since coping is susceptible to therapy in children with epilepsy and their parents,[48] it could be a key approach for preventing problems in social functioning. Psycho-education about the effects of illness and (curative) therapy on the social development of children and social lives of parents may help to prevent problems and lower the threshold to ask for help. Training aimed at coping and self-dependence to help children and parents develop specific skills and compensation strategies should be developed, offered and evaluated.

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Nederlandse samenvatting

Epilepsie is de meest voorkomende chronische hersenaandoening bij kinderen en uit zich in de vorm van aanvallen. Aanvallen ontstaan door een plotselinge, tijdelijke verstoring van de elektrische prikkeloverdracht in de hersenen. Epilepsie is meestal goed behandelbaar met medicijnen (anti-epileptica), die de aanvallen onderdrukken. Bij ongeveer 30% van de kinderen met epilepsie lukt het niet om de aanvallen met medicatie onder controle te krijgen. Bij sommige van deze kinderen – namelijk de groep bij wie de epilepsie 'focaal' is (vanuit één plek ontstaat) – wordt epilepsiechirurgie overwogen. Dit is een hersenoperatie waarbij de bron van de aanvallen in de hersenen wordt weggenomen. Epilepsiechirurgie is alleen een optie wanneer de epileptische bron goed kan worden geïdentificeerd, deze toegankelijk is voor de operatie en deze geen belangrijke functies representeert, zoals bewegen, taal en geheugen. Onderzoeken hebben aangetoond dat epilepsiechirurgie bij goed geselecteerde kandidaten veilig en effectief is. Ongeveer 50–80% van de geopereerde kinderen wordt aanvalsvrij en het algemene cognitieve functioneren (zoals intelligentie) gaat door een dergelijke operatie niet achteruit. Sterker nog, zowel het stoppen van de aanvallen als het stoppen met medicatie, vormen voor een deel van de kinderen de basis voor verdere ontwikkeling.

Er is nog weinig bekend over het sociale functioneren van kinderen en hun ouders voor en na epilepsiechirurgie. Sociaal functioneren is een cruciaal onderdeel van het leven en begint al heel vroeg in de ontwikkeling. Het horen van rustgevende stemmen, oogcontact maken, lachen, spelen, delen, helpen of geholpen worden, relaties aangaan en samenwerken zijn allemaal afhankelijk van sociale interactie. Sociaal functioneren is kwetsbaar bij kinderen met moeilijk behandelbare epilepsie. Aanvallen kunnen gevaarlijk zijn, omdat een aanval het bewustzijn kan verlagen waardoor iemand niet in staat is om te reageren, zoals in het verkeer of in het zwembad. Kinderen met epilepsie hebben enerzijds beperkingen in wat ze mogen (alleen op pad gaan) en kunnen doen (bijvoorbeeld door vermoeidheid), maar er wordt anderzijds juist veel meer van ze verwacht (naar het ziekenhuis gaan, medicatie slikken) dan van gezonde kinderen. Kinderen met epilepsie maken hierdoor minder sociale activiteiten mee, wat niet alleen verdrietig is, maar waardoor zij ook minder sociale ervaringen opdoen om van te leren. De beperkingen en verplichtingen die epilepsie met zich meebrengen hebben niet alleen effect op het kind zelf, maar ook op de andere gezinsleden. Ouders van kinderen met epilepsie hebben grotere kans op angstklachten, depressie en vermoeidheid, wat hun kwaliteit van leven bedreigt.

Epilepsiechirurgie zou, als het tot aanvalsvrijheid leidt, de negatieve gevolgen van epilepsie kunnen verminderen. Aan de andere kant kan epilepsiechirurgie ook een extra bedreiging zijn voor sociaal functioneren, omdat in een groot deel van de operaties hersenstructu-

ren (zoals de amygdala) en netwerken worden verwijderd die betrokken zijn bij 'sociale cognitie'. De term sociale cognitie verwijst naar specifieke hersenfuncties die nodig zijn om te kunnen interpreteren hoe andere mensen zich voelen en wat ze denken, en om te kunnen voorspellen hoe anderen zich gedragen. Voorbeelden van sociale cognitie zijn het interpreteren van gezichtsuitdrukkingen of andere lichaamstaal, het begrijpen van sarcasme en het inzien dat, en waarom, iemand in een bepaalde situatie verdrietig is. Sociale cognitie is nodig om gepast te kunnen reageren in sociale situaties en maakt dus een onmisbaar en essentieel onderdeel uit van sociaal functioneren.

Voor het onderzoek dat in dit proefschrift wordt beschreven hebben we tussen januari 2008 en december 2010 alle kinderen die epilepsiechirurgie ondergingen en hun ouders gevraagd deel te nemen. Ze deden dit door een aantal neuropsychologische taken uit te voeren en daarnaast vragenlijsten in te vullen op het gebied van sociaal functioneren. Dit was een aanvulling op het standaard neuropsychologisch onderzoek dat alle kinderen al ondergingen voor de operatie en 6, 12 en 24 maanden na de operatie. Voor elk kind met epilepsie dat meedeed, deden ook twee gezonde leeftijdsgenoten van hetzelfde geslacht en hun ouders mee.

De hoofdstukken in dit proefschrift beschrijven de onderzoeken naar verschillende sociale aspecten rond epilepsiechirurgie bij kinderen.

In **deel I 'Kinderen'**, wordt beschreven dat kinderen met moeilijk behandelbare epilepsie het slechter doen op taken die sociale cognitie testen vergeleken met gezonde leeftijdsgenoten (hoofdstukken 2 & 3). Dit verschil kwam niet alleen door de lagere intelligentie van kinderen met moeilijk behandelbare epilepsie. De operatie had weinig effect op sociale cognitie; twee jaar na de operatie waren de prestaties op de taken niet slechter dan daarvoor, maar er had ook geen inhaalslag plaatsgevonden. We keken in de patiëntengroep of er specifieke epilepsiekenmerken gerelateerd waren aan de scores op sociale cognitie. We zagen dat hoe jonger het kind was toen de eerste epileptische aanval optrad, of hoe langer het kind al epilepsie had tot de operatie, hoe minder goed ze presteerden op sociale cognitie taken. We vonden ook dat kinderen bij wie de amygdala betrokken was in het operatiegebied (en dus het epilepsiegebied) het minder goed deden dan kinderen bij wie de amygdala niet was verwijderd. Deze relatie met de amygdala kwam echter alleen tot uiting in de studie waarin kinderen vragen over verhalen met een sociale context moesten beantwoorden (hoofdstuk 3) en niet in de studie waarin kinderen emotionele gezichtsuitdrukkingen moesten herkennen (hoofdstuk 2).

We vroegen de kinderen zelf een vragenlijst in te vullen om hun persoonlijkheid in kaart te brengen. Kinderen met moeilijk behandelbare epilepsie hadden hogere scores op

vier van de vijf persoonlijkheidskenmerken dan hun leeftijdsgenoten (hoofdstuk 4). Ze beschreven zichzelf als meer 'inadequaat' (in deze vragenlijst gedefinieerd als het hebben van vage angsten, een laag zelfvertrouwen, en vaak somber zijn), meer 'volhardend' (doorzettingsvermogen), meer 'sociaal inadequaat' (teruggetrokken en verlegen zijn en zich ongemakkelijk voelen in sociale situaties) en meer 'recalcitrant' (anderen wantrouwen, zich afzetten tegen anderen, zich egoïstisch en bezitterig gedragen). De score op 'dominantie' was niet anders dan die van leeftijdsgenoten. Na de operatie nam de score op 'sociale inadequatie' geleidelijk aan af (en werd dus 'beter'). Er konden geen relaties worden aangetoond tussen persoonlijkheidskenmerken en epilepsiekenmerken.

In de literatuurstudie over sociaal functioneren van kinderen voor en na epilepsiechirurgie (**deel III, 'Overzicht'**, hoofdstuk 7) werden de gevonden artikelen vanwege het verschil in aanpak van de onderzoeken ingedeeld in twee categorieën. Een deel van de studies besloeg onderzoek naar sociale cognitie (onderzocht door middel van neuropsychologische taken) en het andere deel onderzocht het meer algemene sociale dagelijkse functioneren van deze kinderen met behulp van vragenlijsten en interviews. De resultaten van de studies benadrukken het risico op problemen in sociale cognitie bij kinderen met moeilijk behandelbare epilepsie en bevestigen de slechts zeer geringe verbetering hierin na epilepsiechirurgie. Ook op het gebied van meer algemeen sociaal functioneren hebben deze kinderen problemen, zoals sociale angst, sociale isolatie en moeite met sociale interacties. Enkele problemen namen af na operatie, maar het merendeel van de kinderen bleef problemen ervaren in sociaal functioneren.

In **deel II 'Ouders'** komt naar voren dat stress gerelateerd aan opvoeding hoger is bij ouders van een kind met moeilijk behandelbare epilepsie dan bij ouders van gezonde leeftijdsgenoten. De scores zijn hoger op alle subschalen van het zogenaamde *kinddomein* van de gebruikte vragenlijst: Stemming, Aanpassing, Afleidbaarheid/hyperactiviteit, Veeleisendheid, Positieve bekrachtiging en Acceptatie (hoofdstuk 5). In het *ouderdomein* was de verhoogde stress terug te zien in drie van de zeven subschalen (Rolrestrictie, Gezondheidsbeleving en Huwelijksrelatie). Dit geeft aan dat de stress bij ouders met name gerelateerd is aan eigenschappen van het kind. Opvoedingsstress nam af na epilepsiechirurgie bij het kind, maar deze afname was niet sterker dan de afname die in de loop der tijd werd gezien bij ouders van gezonde kinderen. Bovendien was de stress twee jaar na de operatie nog altijd hoger dan de normgroep van de vragenlijst. Stress nam het meest af bij ouders van kinderen die aanvalsvrij werden na de operatie en de afname was sterker in de subschalen van het ouderdomein dan van het kinddomein.

We vroegen ouders twee tot vier jaar na epilepsiechirurgie bij hun kind, door middel van vragenlijsten, naar hun eigen psychologische functioneren en hun kijk op het

gezinsfunctioneren (hoofdstuk 6). Moeders rapporteerden problemen op het gebied van 'hostiliteit' (boos, geïrriteerd zijn en veel strijd hebben) en 'communicatie' (ontevreden over hoe ze hun kind begrijpen en vertrouwen, naar hun kind luisteren en empathisch communiceren zonder conflict). Slechts enkele vaders rapporteerden problemen en deze hadden met name betrekking op de 'organisatie' binnen het gezin (ontevreden over hoe het gezinsleven is geregeld en gestructureerd, bijvoorbeeld op gebied van taakverdeling en routine en hoe het gezin omgaat met problemen). De problemen die ouders aangaven waren wederom niet gerelateerd aan epilepsiekenmerken bij het kind. De problemen waren wel gerelateerd aan de leeftijd van het kind en de door ouders gerapporteerde gedragsproblemen van het kind. Gedragsproblemen komen veel voor bij kinderen met epilepsie, hebben negatieve impact op het gezin en het psychisch welzijn van ouders en lossen meestal niet op na epilepsiechirurgie.

Er zijn dus problemen in het sociale functioneren (zowel sociale cognitie als dagelijks sociaal functioneren) van kinderen met moeilijk behandelbare epilepsie en in het sociale functioneren van hun ouders, zowel voor als na epilepsiechirurgie. Epilepsiechirurgie vormt geen extra risico op problemen in sociaal functioneren, maar zorgt ook niet voor volledig herstel. Er zijn maar enkele epilepsiekenmerken gerelateerd aan de sociale problemen. Het vroeg ontstaan van epilepsie, of het lang hebben van epilepsie is gerelateerd aan problemen in sociaal functioneren van de kinderen. Een verklaring hiervoor zou kunnen zijn dat epilepsie schade brengt aan de (ontwikkeling van) hersenstructuren en hersennetwerken die betrokken zijn bij sociale cognitie. Hoe eerder de epilepsie is ontstaan, hoe vroeger deze de ontwikkeling heeft kunnen verstoren. Epilepsie kan ook gezien worden als een gevolg van een onderliggende hersenafwijking. Vroeger optreden van epilepsie is dan een aanwijzing voor een ernstigere hersenafwijking, die een ernstigere verstoring van sociale cognitie veroorzaakt. Dit zou kunnen verklaren waarom er na de operatie geen verslechtering van sociale cognitie optreedt: het verwijderde hersengebied was al aangetast waardoor er geen belangrijke functies in werden aangestuurd. Vroeg ontstaan van epilepsie, zo blijkt uit ander onderzoek, is ook gerelateerd aan stoornissen in andere cognitieve vaardigheden, zowel het algehele cognitieve functioneren – uitgedrukt als intelligentie – als ook de specifieke vaardigheden die nodig zijn bij sociale cognitie, zoals taal en aandacht. Het zou kunnen zijn dat sociale cognitie niet specifiek gestoord is, maar onderdeel is van deze cognitieve problemen. Aan de andere kant zagen wij dat op sommige specifieke taken, zoals geheugen voor gezichten en geheugen voor abstracte tekeningen, de kinderen met epilepsie het niet slechter deden dan de gezonde leeftijdsgenoten. Dit zou erop kunnen duiden dat er toch iets specifieks aan de hand is met de sociale cognitie, maar verder onderzoek is nodig om hier meer helderheid over te verschaffen.

Problemen in algeheel sociaal functioneren zouden voort kunnen komen uit de problemen in sociale cognitie die deze kinderen hebben. Sociale cognitie is immers een voorwaarde om adequaat te reageren in sociale situaties. De medische verbetering (aanvalsvrij worden, medicatie afbouwen) na operatie blijkt maar weinig invloed te hebben op het sociale functioneren, waardoor wij voorstellen de problemen in sociaal functioneren te interpreteren aan de hand van een breder kader, het biopsychosociaal model (zie hoofdstuk 8). Dit model biedt ruimte om naast de medische (biologische) aspecten, ook de sociale en psychologische aspecten van het kind en de ouders te overwegen om hun (sociale) functioneren te begrijpen. Figuur 8.2 (op pagina 152) is een voorbeeld van het model ingevuld voor een kind dat epilepsiechirurgie ondergaat. Naast de medische aspecten hebben kinderen met epilepsie te maken met stigma's en leefregels en met een verhoogde kans op gedragsproblemen, depressie en angst. De drie dimensies overlappen elkaar; de invloeden interacteren. De chroniciteit van moeilijk behandelbare epilepsie maakt dat de invloeden lang aanwezig zijn en lang interacteren waardoor er hardnekkige patronen ontstaan die niet zomaar doorbroken zijn na epilepsiechirurgie. Kinderen met epilepsie hebben voortdurende begeleiding nodig om hun veiligheid te garanderen, waardoor ze beperkt worden in het ontwikkelen van zelfstandigheid. Het stoppen van de aanvallen na chirurgie maakt dat die begeleiding niet meer nodig is vanwege de veiligheid, maar de achterstand in ontwikkeling van zelfstandigheid is met een operatie niet opgelost. Minder hebben kunnen deelnemen aan sociale situaties door aanvallen, vermoeidheid, ziekenhuisbezoeken of andere factoren hebben geleid tot verminderde mogelijkheden om van te leren, wat kan hebben geleid tot onderontwikkelde sociale cognitie en sociale vaardigheden. De chronische epilepsie van het kind heeft ook invloed op het leven van de ouders. Ouders van kinderen met epilepsie hebben een verhoogd risico op depressie, angst en stress. De continue begeleiding die ouders hun kind met epilepsie bieden, verandert het leven van de ouders. Slecht slapen, minder kunnen werken, minder vrijheid voelen om uit te gaan en niet in staat zijn om de vrijheid van het kind te vergroten zoals dat bij de leeftijd zou passen, zijn voorbeelden die om aanpassingen van ouders vragen. Wanneer de epilepsie eenmaal succesvol is behandeld, neemt het beroep wat op ouders wordt gedaan af, maar de aanpassingen zijn ingesleten en moeilijk te veranderen. Ouders kunnen zich overbodig voelen en worstelen met het vinden van een nieuwe rol. De processen van het kind en de ouders beïnvloeden elkaar sterk, waardoor het extra moeilijk is om een nieuwe balans te vinden.

Het is belangrijk dat naast de positieve aspecten van aanvalsvrij worden na epilepsiechirurgie, ook aandacht wordt geschonken aan de mogelijke problemen die bij het kind, de ouders en in het gezin blijven bestaan. Wij denken dat het zinvol is om gezinnen nog beter voor te bereiden op de periode van herstel na epilepsiechirurgie, door psycho-educatie

te geven over de invloed van epilepsie en behandeling op de sociale ontwikkeling van kinderen en het sociale leven van ouders. Dit zou tevens de drempel kunnen verlagen om hulpverlening in te schakelen voor gezinnen die extra hulp nodig hebben. Mogelijk kan een training helpen om extra vaardigheden aan te leren op gebied van coping en zelfstandigheid om het sociale functioneren van kinderen na epilepsiechirurgie en hun ouders te optimaliseren.

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[1] Stok achter de deur.

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About the author

Curriculum Vitae

Olga Braams werd geboren op 21 februari 1979 in Son en Breugel. Zij groeide op in dit kleine Brabantse dorp vlakbij Eindhoven. In 1998 behaalde zij het VWO-diploma aan het Eckart college te Eindhoven. Na uitloten voor de opleiding geneeskunde, startte zij met de studie psychologie aan de Universiteit van Utrecht die zij vervolgde in de richting neuropsychologie. Zij liep stage bij de sector neuropsychologie van het Wilhelmina Kinderziekenhuis en kon tijdens het afronden van de scriptie aanblijven als onderzoeksassistent voor een wetenschappelijk onderzoek. In 2005 behaalde zij haar diploma neuropsychologie en begon zij parttime als psychologisch medewerker bij de sector neuropsychologie van het WKZ. In 2008 startte zij naast deze functie met het in dit proefschrift beschreven onderzoek, dat plaatsvond in het WKZ en in het Bio Research Centre for Children (BRCC) in Arnhem. Naast haar werkzaamheden in het ziekenhuis begeleidde zij pubers met een psychiatrische diagnose tijdens logeerweekenden en trad zij toe tot het bestuur van de Nederlandse Vereniging voor Neuropsychologie. In 2012 begon zij aan de opleiding tot gezondheidszorgpsycholoog en verschoven haar werkzaamheden van het beantwoorden van voornamelijk neuropsychologische vraagstukken, naar bredere medisch psychologische hulpvragen. In 2016 mocht zij zich officieel gezondheidszorgpsycholoog noemen en kreeg zij een aanstelling bij afdeling medische psychologie en maatschappelijk werk van het WKZ, met neurologie en cystic fibrosis als haar speciale aandachtsgebieden. Naast haar enthousiasme voor het werken met kinderen en jongeren in het ziekenhuis, heeft zij een groeiende interesse voor het welzijn van collega's in de zorg. Zij initieerde een project voor begeleide interversie onder zorgverleners in het WKZ en startte met werkzaamheden als co-trainer in de Peer Support training en als coach voor geneeskundestudenten. Zij woont samen met Eelco in Kerk Avezaath.

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Stellingen

behorende bij het proefschrift

Social *matters* before and after epilepsy surgery in children

1. Kinderen met moeilijk behandelbare epilepsie hebben een verhoogd risico op problemen in sociale cognitie en algemeen sociaal functioneren. *Dit proefschrift*
2. Epilepsiechirurgie vormt geen extra risico op problemen in de sociale cognitie van kinderen. *Dit proefschrift*
3. Ouders van een kind met moeilijk behandelbare epilepsie hebben meer opvoedingsgerelateerde stress dan ouders van gezonde leeftijdsgenoten. *Dit proefschrift*
4. Epilepsiechirurgie zorgt niet voor een volledig herstel van problemen in sociaal functioneren. *Dit proefschrift*
5. Epilepsievrijheid duurt tot de volgende aanval.
6. Ingesleten patronen hebben tijd nodig om te slijten.
7. Het werk houdt niet op door het te doen. *Mijntje van der Linde*
8. Life is like an onion: you peel it off one layer at a time, and sometimes you weep. *Carl Sandburg*
9. Hoe dun de pannenkoek ook is, hij heb altijd twee kanten. *Ellie Lust*
10. Hoe eerder je achterloopt, hoe langer de tijd om in te halen.
11. Als we wisten wat we deden, heette het geen onderzoek. *Albert Einstein*

Olga Braams
Utrecht, 9 mei 2019