Original article

Epileptic Disord 2019; 21 (2): 166-76

Epilepsy surgery in children: no further threat to theory of mind

Olga B. Braams [1,2], Joost Meekes [3], Onno van Nieuwenhuizen [2], Renske Schappin [1], Peter C. van Rijen [2], Els M.A. Blijd-Hoogewys [4], Maarten Steffers [5], Kees P.J. Braun [2], Aag Jennekens-Schinkel [2]

[1] Department of Pediatric Psychology and Social Work, University Medical Center Utrecht
[2] Brain Center Rudolf Magnus, Departments of Child Neurology and Neurosurgery, University Medical Center Utrecht
[3] Neuropsychology Lab, Oldenburg University Oldenburg, Oldenburg, Germany
[4] Inter-Psy Groningen, Groningen
[5] Department of Psychiatry, University Medical Center Utrecht, The Netherlands

Received May 02, 2018; Accepted February 20, 2019

ABSTRACT – *Aims.* To investigate 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, one and two 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 analyse differences between patients and controls. The association between ToM and demographic, epilepsy and surgical variables was 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 favourable effect on ToM. Later epilepsy onset and temporal origin of epilepsy were associated with higher (better) ToM scores relative to earlier epilepsy onset and extratemporal epilepsy (including hemispherotomy in one case). Children in whom the amygdala was resected had worse ToM scores. *Conclusion.* Children with refractory epilepsy have a ToM deficit that may not be accounted for by 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. Finally, the amygdala is implicated in ToM deficit. Patients and their parents should be educated about the possible consequences of epilepsy with regards to the development of social cognition and should be guided in order to help improve ToM.

Key words: theory of mind, social cognition, child, refractory epilepsy, epilepsy surgery

Correspondence:
Olga Braams
University Medical Center Utrecht,
Department of Pediatric Psychology and Social Work,
University Medical Center Utrecht,
PO Box 85090, 3508 AB Utrecht,
The Netherlands
<obraams@umcutrecht.nl>

doi:10.1684/epd.2019.1053

Theory of mind (ToM) is an important ability for social functioning from early childhood onwards. ToM enables one to be able to attribute "mental states" such as feelings, intentions, beliefs, and desires to others and to oneself. ToM allows one to predict behaviour of others and to adapt one's own actions when interacting with others (Frith and Frith, 2006; Wellman, 2014). For example, when a girl is nearly three years old and 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. This latter ability typically develops between the ages of three to five years (Pons *et al.*, 2004). A famous example of a ToM task is the "Sally and Anne" test (Wimmer and Perner, 1983; Baron-Cohen *et al.*, 1985). 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 where it actually is, in the 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 as a ToM ability (Blijd-Hoogewys *et al.*, 2008).

Language comprehension is highly related to ToM functioning and can be considered an essential skill for developing ToM (Astington and Baird, 2005; Villiers and Villiers, 2014).

ToM deficits have often been reported in adults with epilepsy, especially in patients with temporal lobe epilepsy (Broicher *et al.*, 2012; Wang *et al.*, 2015; Steward *et al.*, 2016). Several neuroanatomical regions and networks have been suggested to be involved in ToM, including parts of the prefrontal cortex and superior temporal sulcus (for a review, see Carrington and Bailey, 2009). The amygdala, in particular, has been described as crucial in the cerebral mediation of ToM (Fine *et al.*, 2001; Shaw *et al.*, 2004). However, surgery to treat temporal lobe epilepsy in adults appears to neither improve nor worsen ToM functioning (Giovagnoli *et al.*, 2016).

Despite its developmental significance in everyday functioning, research on ToM in paediatric epilepsy patients is scarce. ToM is vulnerable even in children with "epilepsy only" and this cannot be explained by lower intelligence (Lew *et al.*, 2015; Lunn *et al.*, 2015). Furthermore, a later onset of epilepsy is associated with better ToM functioning, whereas antiepileptic drug use is not related to ToM functioning (Lew *et al.*, 2015; Lunn *et al.*, 2015). Effects of surgical treatment of epilepsy surgery on ToM in children remain to be established. From a previous study, we learnt that epilepsy surgery causes a transient decrease in recognition of facially expressed emotions, one of the abilities that underlies ToM (Blijd-Hoogewys and Geert, 2017), but only in children younger than 13 years at the time of surgery (Braams *et al.*, 2015).

Given the importance of ToM in social functioning, the question whether epilepsy surgery affects the development of ToM over and beyond the deficit inflicted by epilepsy *per se* is crucial for adequate pre-surgical counselling 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 differences in ToM over time (before surgery and 0.5, one and two years after surgery) as well as possible associations between ToM and demographic (age at assessment, intelligence, and sex) and epilepsy and surgical variables (epilepsy onset age, side and area of surgery, aetiology, resection of the amygdala [by amygdalohippocampectomy], antiepileptic drug use, and post-surgical seizure status).

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 (Meekes *et al.*, 2013, 2014; Braams *et al.*, 2015). The Institutional Review Board of the University Medical Center of Utrecht approved the study. Parents of all children and all children above the age of 12 years provided written informed consent.

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 for the ToM instrument. Five of these children could not perform the ToM instrument due to poor cognitive functioning and/or severe behavioural problems; one child belonged to an ethnic minority and 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 twice post-surgically (at 0.5, one or two years after surgery) (see *table 1* for

Table 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)
Age at epilepsy onset		3.8 (2.6)
Duration of epilepsy		3.5 (1.7)
Number of AEDs (*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)
Aetiology (*n*)		
Cerebral tumour	5[1]	8.1 (2.6)
MCD	6	6.2 (1.8)
HS	2	5.4 (1.8)
Other	2[2]	9.2 (1.6)
Surgical area (*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*)		
Unresected	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. [1]Ganglioglioma (*n*=3), oligodendroglioma (*n*=1), dysembryoplastic neuro-epithelial tumour (DNET) (*n*=1). [2]Cerebral infarction (*n*=1); cavernoma (*n*=1). *Defined as complete seizure freedom for two years following surgery.

demographic and epilepsy variables, 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 at 0.5, one, and two years after the intervention. The controls were assessed at similar intervals.

Instruments

Theory of mind (ToM) storybooks

The ToM storybooks have been designed to assess ToM abilities in children between four and 12 years of age (Blijd-Hoogewys *et al.*, 2008). This instrument targets ToM development prior to the age of four and is applicable beyond that age. Norm scores are available from the age of three up to 12 years and the instrument 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 colourful and animated with doors that open and separate response cards with faces expressing emotions that can be selected and placed on characters (*for an example*, see *appendix 1*). In accordance 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 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 a mean of 100 and SD equal to 15. Higher scores indicate better ToM. Scores for the ToM storybooks correlate strongly with intelligence and language skills (Blijd-Hoogewys *et al.*, 2008). 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) (Blijd-Hoogewys *et al.*, 2008; Bulgarelli *et al.*, 2015).

Intelligence
Intelligence was assessed using a range of instruments, selected in accordance with the mandate of best clinical practice (*e.g.* Wechsler Intelligence Scale for Children-III) (Wechsler, 2002; Kort *et al.*, 2005). 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 (Blijd-Hoogewys *et al.*, 2008; Villiers and Villiers, 2014).

Data management and analyses

Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM, 2011). Differences between patients and controls (as groups) were examined using Linear Mixed Models (LMM) using age at assessment and VIQ as covariates and group, time (pre-surgery and 0.5, one and two years after surgery), and sex as factors. The advantage of LMM over analysis of repeated measures of variance is their capacity to handle small samples and unequal time intervals between measurements (*i.e.* 0.5 years between the first two postoperative measurements and one 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 age at epilepsy onset, time (pre-surgery and 0.5, one and two years after surgery), and number of antiepileptic 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), aetiology (tumour/malformation of cortical development/hippocampal sclerosis/other), and seizure freedom (no seizures during the two years of follow-up after surgery; yes/no) were included as factors in the LMM analysis. A further explorative LMM analysis focused on, besides time, variables corresponding to the first epileptic seizure, *i.e.* onset age, side and area of epilepsy focus (and of surgery), aetiology, and resection of the amygdala. VIQ was not included in these analyses as it may conceal other possible associations with ToM-Q. LMM analyses with VIQ, rather than ToM-Q, were performed in the same way in order to clarify the degree of VIQ and ToM-Q prediction based on the same variables (see *supplementary tables 1, 2*). Due to the small size of the patient sample, interactions were not analysed. *P* values <0.05 were considered statistically significant.

Results

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

Figure 1 shows scores for ToM-Q and VIQ of patients and control children over the two-year period.
LMM analysis (*table 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; $p<0.001$]).
VIQ significantly positively correlated with ToM-Q. The significant association between group and age at assessment indicates that, for control children, ToM-Q was age-independent (which was to be expected since ToM-Q is age-normed), whereas in patients, ToM-Q increased with age (*figure 2*). There was no significant relation between ToM-Q and either (follow-up) time or sex.

Epilepsy variables associated with ToM

For the group of patients, exploratory LMM analysis (*table 3*) showed that epilepsy onset age and ToM-Q were significantly related; patients who were older at epilepsy onset obtained higher ToM-Qs. Also, patients with epilepsy and surgery restricted to the temporal area had higher ToM-Qs than children who underwent extra-temporal surgery or hemispherotomy (*table 3*). Furthermore, differences between the assessments before and after surgery were not statistically significant. The relationships between ToM-Q and the other variables (left or right side of epilepsy/surgery, resection of amygdala, aetiology, AED number, and seizure freedom) were not significant.
LMM analysis was narrowed down to those variables corresponding to the first epileptic seizure (onset age, side, area, aetiology, and resection of the amygdala) and revealed that, apart from age at onset and surgical area, resection of the amygdala was related to ToM-Q; children whose amygdala was not included in the resection obtained higher ToM-Qs (*table 4*). Again, the relationship between ToM-Q and time (pre-surgery and 0.5, one and two years after surgery), ToM-Q and the side of resection, and ToM-Q and aetiology were not significant.

Additional correlations
In order to interpret the results properly, it was necessary to further study the relationships between some other variables. First, because age at onset was related

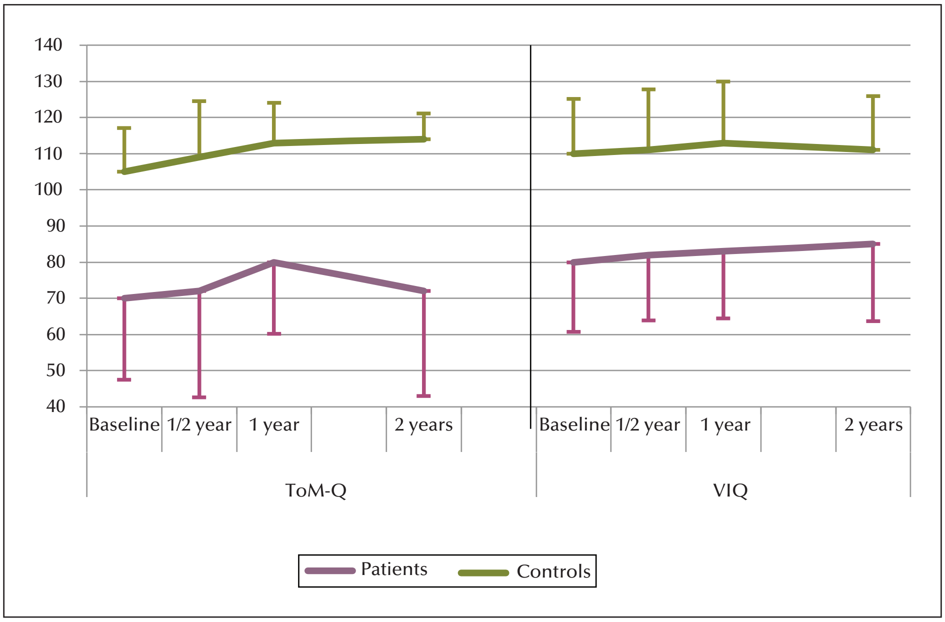


Figure 1. Two-year follow-up scores of ToM-Q and VIQ for patients and healthy peers.

to ToM-Q and because age at onset and age of the child are related, we analysed the correlation between age at surgery and epilepsy onset which was shown to be strong (Pearson r=0.71; $p<0.001$).

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 surgery had a mean VIQ of 69 (SD: =15) and a mean epilepsy onset age of 3.7 years (SD: 2.7).

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 resection.

Table 2. LMM analysis of ToM-Q according to group, sex, time, and age, and correlation between group and age (corrected for VIQ).

	Estimate	95%CI Lower bound	Upper bound	F	df	*p*
Intercept	35.84	13.04	58.63	1.307	65.64	0.257
Group[a]	-53.56	-74.53	-32.60	26.239	53.88	<0.001
Sex[b]	3.07	-2.49	8.63	1.254	36.62	0.270
Time*	0.11	-2.97	3.20	0.005	57.12	0.942
Age at assessment	5.55	3.65	7.45	30.102	41.57	<0.001
Group age at assessment[c]	4.25	1.89	6.61	13.052	55.94	0.001
VIQ	0.55	0.40	0.70	55.175	75.56	<0.001

CI: Confidence interval. [a]Patients (control group is reference). [b]Girls (boy group is reference). *Time: presurgical and 0.5, one and two years post-surgery. [c]Patient group (control group is reference).

Table 3. LMM analysis of ToM-Q with time, side of surgery, surgical area, status amygdala, aetiology, AED number, seizure freedom and age at epilepsy onset.

	Estimate	95% CI Lower bound Upper bound		F	df	*p*
Intercept	71.4	42.9	100	22.065	21.53	<0.001
Time (years)*	0.96	-8.07	9.99	.049	20.14	0.827
Side of surgery[a]	-10.7	-27.5	6.07	2.680	5.05	0.162
Amygdala status[b]	33.9	-0.98	68.7	5.369	6.73	0.055
Surgical area[c]	-30.62	-53.8	-7.49	10.694	5.77	0.018
Aetiology[d]				1.460	5.68	0.321
Cerebral tumour	-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 (years)	7.42	3.39	11.45	21.553	5.34	.005

CI: Confidence interval. *Time: presurgical and 0.5, one and two 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.

Table 4. LMM analysis of ToM-Q with time and illness variables: side of surgery, surgical area, status amygdala, aetiology and epilepsy onset age.

	Estimate	95% CI Lower bound Upper bound		F	df	*p*
Intercept	67.3	44.9	89.8	34.038	11.28	0.000
Time*	3.53	-4.04	11.09	0.994	14.38	0.335
Side of surgery[a]	-12.1	-27.2	3.07	3.618	6.72	0.101
Amygdala status[b]	34.7	1.25	68.1	5.425	9.46	0.043
Surgical area[c]	-34.9	-54.8	-15.1	17.747	6.57	0.005
Aetiology[d]				2.134	7.43	0.180
Cerebral tumour	-32.1	-70.3	6.01			
MCD	-20.4	-55.2	14.4			
HS	-20.5	-47.6	6.7			
Epilepsy onset age (years)	7.49	3.67	11.31	20.964	7.483	0.002

CI: Confidence interval. *Time: presurgical and 0.5, one and two 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.

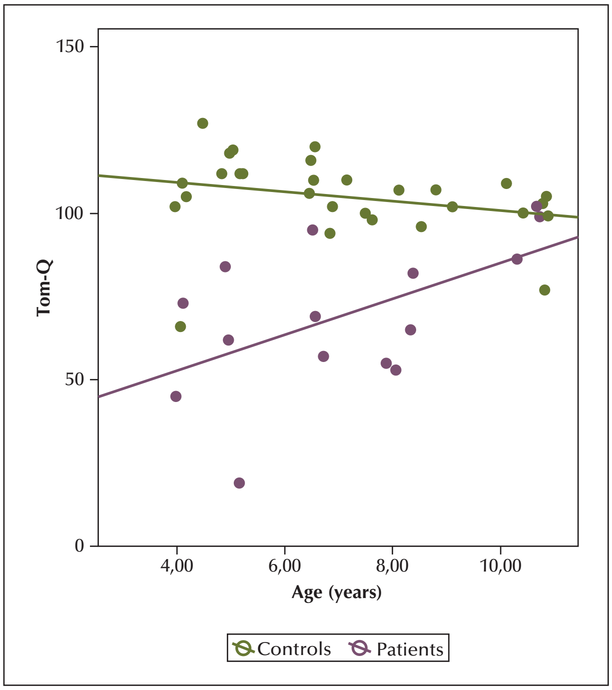


Figure 2. Relationship between ToM-Q and age for patients and controls.

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 at the benign end of the severity spectrum) have recently been shown to have a ToM deficit (Lew *et al.*, 2015; Lunn *et al.*, 2015). Controlling for 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 unravelled as an effect of age at epilepsy onset; children with later epilepsy onset had better ToM-Q. Patients with early-onset epilepsy were assessed at a younger age; the correlation between age at assessment and age at onset was significant (Pearson correlation: 0.735; p=0.002). The relationship between age at onset and ToM-Q was confirmed by the analysis in patients only, for whom ToM-Q was related to several variables; as discussed below.

Surgical treatment does not affect ToM-Q

Our primary interest concerned the effects of epilepsy surgery on ToM. Arguably, the effect could be favourable if cessation of seizures and discontinuation of AEDs enable ToM to develop without further disturbance from epilepsy, or unfavourable if surgery poses a risk to ToM development. Using the four assessment times as a variable, surgery *per se* was shown to not have a significant effect on ToM-Q. This is in contrast to what we previously reported; the recognition of facially expressed emotions -although transiently expressed- was indeed affected by surgery in a group of younger (age <13 years) patients (Braams *et al.*, 2015). The two tasks, recognizing facially expressed emotions and ToM, share the requirement to interpret pictured emotions. An important difference, however, is that the test to recognise 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 require 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.* area of origin of seizures and hence surgical area], resection of amygdala, aetiology, AED number, and 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 storybooks than children with frontal, centro-parietal, or 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 1*).

Early epilepsy onset was associated with more deficient ToM. Early-onset age has often been reported to be related to impaired cognitive functioning (Vendrame *et al.*, 2009; Berg *et al.*, 2012) and social cognition (Morou *et al.*, 2018). In her targeted review, Giovagnoli discussed the impact that epilepsy may have on the underlying neural circuitry associated with ToM. She suggested that patients with early-onset epilepsy are at an increased risk of either losing or not developing ToM abilities (Giovagnoli, 2014). It could 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 the environment as well. Early onset implies early parental concerns for the child, early special interactions with the child, and early epilepsy-related restrictions imposed upon the child (Carpay *et al.*, 1997). 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 oneself to a lesser degree than healthy peers (Hughes and Dunn, 1998). The fact that ToM-Q did not normalise 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.

In an effort 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- were both treatment-independent. Excluding treatment variables (AED number and seizure freedom) from the LMM analysis revealed the significance of resection of the amygdala. Children whose amygdala was not included in the resection had a better ToM-Q than children whose amygdala was resected (*i.e.* in children in whom the epileptogenic zone included the amygdala). Visual scrutiny of the data showed that two of the children who received surgery in the temporal lobe not involving the amygdala performed better on ToM storybooks than the four children in whom temporal lobe intervention included the amygdala. The child who had undergone a hemispherotomy performed worse on ToM storybooks than the eight other children who had undergone extra-temporal surgery (see *supplementary figures 1, 2*).

Research on the role of the amygdala in ToM has yielded contradictory findings. Spunt *et al.* reported unimpaired ToM in adult patients with bilateral amygdala lesions and concluded that the amygdala is not necessary for the cortical mediation of ToM in adulthood (Spunt *et al.*, 2015). In contrast, Stone *et al.*, based on a case study, argued that the amygdala continues to play a critical "on-line" role in ToM after the development of this ability (Stone *et al.*, 2003). Shaw *et al.* reported that early (*i.e.* before the age of 16 years), but not late, damage to the amygdala impairs ToM and postulated that the amygdala may be necessary for low-level tasks 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 (Shaw *et al.*, 2014). Although based on small numbers, our study indicates that inclusion of the amygdala in surgical resection (*i.e.* the amygdala may have been affected by the epilepsy or underlying aetiology prior to surgery) has a negative effect on ToM in children.

Limitations and strengths

The population of children who undergo epilepsy surgery is heterogeneous with regards to variables such as age, intelligence, aetiology, and side and site of surgery. This heterogeneity is reflected in our sample. Furthermore, the sample is small, which is partly related to 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. Firstly, we wanted to evaluate ToM in patients against a background of typical development, and secondly, a comparison with clinical groups would entail unwanted influences from sets of variables associated with a particular illness. We consider the use of two age- and sex-matched control children per patient recruited from divergent social strata as a methodological strength.

Conclusion

ToM appears to be affected by variables associated with the origin of epilepsy, such as the cerebral area (rather than the side) of the epileptic focus and onset age. The development of ToM is threatened by these variables, but barely influenced by treatment (whether surgery or antiepileptic drug use) or seizure freedom. This renders ultimate ToM functioning in 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 the possible consequences of epilepsy with regards to the development of 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 labelling their own emotions and thoughts as well as those of others, which may improve their ToM abilities (Hughes and Dunn, 1998). □

Key points

- Children with refractory epilepsy have poorer ToM than controls.
- Epilepsy surgery neither worsens nor improves ToM functioning.
- Older age at epilepsy onset is related to better ToM relative to younger onset age.
- Epilepsy affecting the temporal lobe is related to better ToM compared to extra-temporal epilepsy.
- The relationship between ToM and the amygdala requires further study.

Supplementary data.
Supplementary material and summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
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. This work was supported by the Dutch Epilepsy Foundation (Nederlands Epilepsie Fonds, NEF), Bio Research Center for Children (BRCC), and the Epilepsies of Childhood Foundation (EPOCH).
None of the authors have any conflict of interest to declare.

References

Astington JW, Baird JA. *Why language matters for theory of mind*. New York: Oxford University Press, 2005.

Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a 'theory of mind'? *Cognition* 1985; 21: 37-46.

Berg AT, Zelko FA, Levy SR, Testa FM. Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes. A prospective cohort study. *Neurology* 2012; 79: 1384-91.

Blijd-Hoogewys EMA, van Geert PLC. Non-linearities in theory-of-mind development. *Front Psychol* 2017; 7: 1970.

Blijd-Hoogewys EMA, van Geert PLC, Serra M, Minderaa RB. Measuring theory of mind in children. Psychometric Properties of the ToM Storybooks. *J Autism Dev Disord* 2008; 38: 1907-30.

Braams O, Meekes J, van Nieuwenhuizen J, *et al*. Two years after epilepsy surgery in children: Recognition of emotions expressed by faces. *Epilepsy Behav* 2015; 51: 140-5.

Broicher SD, Kuchukhidzeb G, Grunwalda T, Krämer G, Kurthen M, Jokeit H. 'Tell me how do I feel' -Emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy. *Neuropsychologia* 2012; 50: 118-28.

Bulgarelli D, Testa S, Molina P. Factorial structure of the 'ToM Storybooks': a test evaluating multiple components of theory of mind. *Br J of Dev Psychol* 2015; 33: 187-202.

Carpay HA, Vermeulen J, Stroink H, *et al*. Disability due to restrictions in childhood epilepsy. *Dev Med Child Neurol* 1997; 39: 521-6.

Carrington SJ, Bailey AJ. Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Hum Brain Mapp* 2009; 30: 2313-35.

Fine C, Lumsden J, Blair RJ. Dissociation between 'theory of mind' and executive functions in a patient with early left amygdala damage. *Brain* 2001; 124: 287-98.

Frith CD, Frith U. The neural basis of mentalizing. *Neuron* 2006; 50: 531-4.

Giovagnoli AR. The importance of theory of mind in epilepsy. *Epilepsy Behav* 2014; 39: 145-53.

Giovagnoli AR, Parente A, Didato G, Deleo F, Villani F. Expanding the spectrum of cognitive outcomes after temporal lobe epilepsy surgery: a prospective study of theory of mind. *Epilepsia* 2016; 57: 920-30.

Hughes C, Dunn J. Understanding mind and emotion: longitudinal associations with mental-state talk between young friends. *Dev Psychol* 1998; 34: 1026-37.

IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp; 2011.

Kort W, Schittekatte M, Dekker PH, Verhaeghe P, Compaan EL, Vermeir G. *WISC-III-NL. Handleiding en verantwoording*. London: The Psychological Corporation, 2005.

Lew AR, Lewis C, Tomlin P, *et al*. Social cognition in children with epilepsy in mainstream education. *Dev Med Child Neurol* 2015 ; 57 : 53-9.

Lunn J, Lewis C, Sherlock C. Impaired performance on advanced theory of mind tasks in children with epilepsy is related to poor communication and increased attention problems. *Epilepsy Behav* 2015; 43: 109-16.

Meekes J, Braams O, Braun KPJ, Jennekens-Schinkel A, van Nieuwenhuizen O. Verbal memory after epilepsy surgery in childhood. *Epilepsy Res* 2013; 107: 146-55.

Meekes J, Braams OB, Braun KPJ, *et al*. Visual memory after epilepsy surgery in children: a standardized regression-based analysis of group and individual outcomes. *Epilepsy Behav* 2014; 36: 57-67.

Morou N, Papaliagkas V, Markouli E, *et al*. Theory of mind impairment in focal versus generalized epilepsy. *Epilepsy Behav* 2018; 88: 244-50.

Pons F, Harris PL, de Rosnay M. Emotion comprehension between 3 and 11 years: developmental periods and hierarchical organization. *Eur J Dev Psy* 2004; 1: 127-52.

Shaw P, Lawrence EJ, Radbourne C, Bramham J, Polkey CE, David AS. The impact of early and late damage to the human amygdala on 'theory of mind' reasoning. *Brain* 2004; 127: 1535-48.

Spunt RP, Elison JT, Dufour N, Hurlemann R, Saxe R, Adolphs R. Amygdala lesions do not compromise the cortical network for false-belief reasoning. *Proc Natl Acad Sci USA* 2015; 112: 4827-32.

Steward E, Catroppa C, Lah S. Theory of mind in patients with epilepsy: a systematic review and meta-analysis. *Neuropsychol Rev* 2016; 26: 3-24.

Stone VE, Baron-Cohen S, Calder A, Keane J, Young A. Acquired theory of mind impairments in individuals with bilateral amygdala lesions. *Neuropsychologia* 2003; 41: 209-20.

Vendrame M, Alexopoulos AV, Boyer K, *et al*. Longer duration of epilepsy and earlier age at epilepsy onset correlate with impaired cognitive development in infancy. *Epilepsy Behav* 2009; 16: 431-5.

Villiers JG, Villiers PA. The role of language in theory of mind development. *Top Lang Disord* 2014; 34: 313-28.

Wang WH, Shih YS, Yu HY, *et al*. Theory of mind and social functioning in patients with temporal lobe epilepsy. *Epilepsia* 2015; 56: 1117-23.

Wechsler D. *Wechsler Intelligence Scale for Children*, 3rd ed.. Lisse: Harcourt Test Publishers, 2002.

Wellman HM. *Making Minds: How Theory of Mind Develops*. New York: Oxford University Press, 2014.

Wimmer H, Perner J. Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception. *Cognition* 1983; 13: 103-28.

TEST YOURSELF

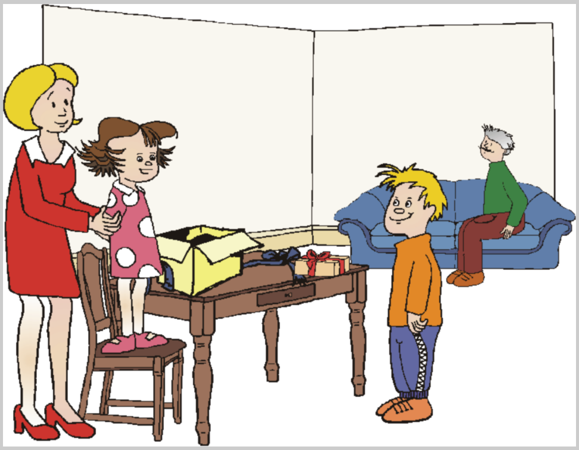
(1) How do ToM abilities in children with refractory epilepsy before epilepsy surgery relate to those in healthy peers?

(2) Does epilepsy surgery affect ToM abilities in children?

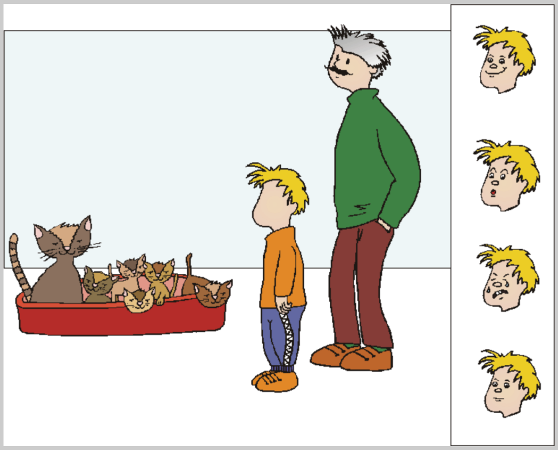
(3) How do epilepsy and surgery variables relate to ToM in children who are candidates for epilepsy surgery?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Appendix 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's house who has kittens.
Sam wants to take a kitten home.
Daddy says they can't.
What will be the expression on Sam's face?