



## Perinatal thalamic injury: MRI predictors of electrical status epilepticus in sleep and long-term neurodevelopment

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### ABSTRACT

**Objective:** Perinatal thalamic injury is associated with epilepsy with electrical status epilepticus in sleep (ESES). The aim of this study was to prospectively quantify the risk of ESES and to assess neuroimaging predictors of neurodevelopment.

**Methods:** We included patients with perinatal thalamic injury. MRI scans were obtained in the neonatal period, around three months of age and during childhood. Thalamic and total brain volumes were obtained from the three months MRI. Diffusion characteristics were assessed. Sleep EEGs distinguished patients into ESES (spike-wave index (SWI) > 85%), ESES-spectrum (SWI 50–85%) or no ESES (SWI < 50%). Serial Intelligence Quotient (IQ)/Developmental Quotient (DQ) scores were obtained during follow-up. Imaging and EEG findings were correlated to neurodevelopmental outcome.

**Results:** Thirty patients were included. Mean thalamic volume at three months was 8.11 (± 1.67) ml and mean total brain volume 526.45 (± 88.99) ml. In the prospective cohort ( $n = 23$ ) 19 patients (83%) developed ESES (-spectrum) abnormalities after a mean follow-up of 96 months. In the univariate analysis, larger thalamic volume, larger total brain volume and lower SWI correlated with higher mean IQ/DQ after 2 years (Pearson's  $r = 0.74$ ,  $p = 0.001$ ; Pearson's  $r = 0.64$ ,  $p = 0.005$ ; and Spearman's  $\rho = -0.44$ ,  $p = 0.03$ ). In a multivariable mixed model analysis, thalamic volume was a significant predictor of IQ/DQ (coefficient 9.60 [ $p < 0.001$ ], i.e., corrected for total brain volume and SWI and accounting for repeated measures within patients, a 1 ml higher thalamic volume was associated with a 9.6 points higher IQ). Diffusion characteristics during childhood correlated with IQ/DQ after 2 years.

**Significance:** Perinatal thalamic injury is followed by electrical status epilepticus in sleep in the majority of patients. Thalamic volume and diffusion characteristics correlate to neurodevelopmental outcome.

### 1. Introduction

Perinatal thalamic injury can be the consequence of hemorrhage, ischemia or infection. Initial presentation in the neonatal period is often with lethargy and seizures. Cranial ultrasound generally reveals signs of thalamic injury and MRI is used to confirm the diagnosis and assess possible etiologies. Long-term neurodevelopmental outcome varies from normal to severe intellectual disability (Guzzetta et al., 2005;

Kersbergen et al., 2013; Zubiaurre-Elorza et al., 2012; Kersbergen et al., 2011; Merlini et al., 2017). After a seizure-free interval, epilepsy often recurs in childhood. Several studies have shown an association between perinatal thalamic injury and epilepsy with electrical status epilepticus in sleep (ESES) (Guzzetta et al., 2005; Kersbergen et al., 2013; Fernández et al., 2012). How perinatal thalamic injury may cause ESES is unclear. Several studies suggested that loss of physiological thalamocortical interaction leads to pathological synchronized activity in

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NREM-sleep as well as loss of control over the developing cortico-cortical network (Siniatchkin et al., 2010; Bartolini et al., 2016; Leal et al., 2018).

Epileptic encephalopathy with ESES is characterized by sleep-induced epileptiform activity accompanied by acquired neurodevelopmental deficits in children over 2 years of age (Patry et al., 1971; Landau and Kleffner, 1957). Their sleep-EEG shows abundant epileptic discharges with a spike-wave index (SWI) of at least 50% (Scheltens-De Boer, 2009). ESES resolves spontaneously during puberty, while the developmental deficits generally persist afterwards. Early detection and prompt treatment initiation may improve neurodevelopmental outcome (Nickels and Wirrell, 2008; Van Den Munckhof et al., 2015).

To the best of our knowledge it is not yet known, what proportion of patients with perinatal thalamic injury will develop epilepsy with ESES. We were able to address this question because these children are routinely seen in the follow-up clinic by a neonatologist and have interval EEGs in our center. In addition, early biomarkers for long-term neurodevelopment after perinatal injury were lacking and we aimed to study whether MRI results at three months and thalamic diffusion characteristics can predict neuropsychological assessment test results.

The aims of the current study were to: 1. quantify the proportion of children with perinatal thalamic injury that eventually develop epilepsy with ESES and ESES-spectrum in a prospectively followed cohort, 2. identify imaging predictors for the occurrence of ESES(-spectrum) and for the severity of neurodevelopmental abnormalities. 3. explore whether DTI characteristics may reveal a possible mechanism that explains the occurrence of ESES and neurodevelopmental deficits after thalamic injury.

## 2. Methods

### 2.1. Patient selection

We included patients with MRI-documented perinatal thalamic injury who were followed until at least 2 years of age and underwent at least one sleep EEG recording. Some of the included patients were also reported in a previous study (Kersbergen et al., 2013).

Subgroups were defined for the purpose of answering different research questions:

- 1) A *prospectively followed cohort* of consecutive patients who were diagnosed with perinatal thalamic injury between 2000 and 2015 and followed in our center from the neonatal period onwards. As part of routine clinical care in our hospital, these children undergo repeated screening of cognitive functioning by a neonatologist or pediatric neurologist, and undergo at least one sleep EEG after the age of two years. MRI scans are made in all children during the neonatal period, at around 3 months of age, and in the majority once again in childhood. Although the patients were not prospectively included in this study at the time of diagnosis of thalamic injury, they were prospectively followed according to our clinical protocol. This cohort was used to quantify the proportion of children with perinatal thalamic injury that developed epilepsy with ESES during follow-up.
- 2) Patients who were referred to our center during childhood with a history of perinatal thalamic injury – some of whom were referred because of epilepsy or ESES, diagnosed elsewhere. These patients were only included in this study if MRIs and EEG follow-up were available. This group of patients was added to the first cohort to correlate imaging findings from the neonatal period with neurodevelopment during follow-up. As they were not prospectively followed in our center, incidence of ESES could not be assessed in these patients.

### 2.2. Data collection

Clinical characteristics were collected from the neonatal period

(gestational age, pregnancy/delivery complications, Apgar scores, etiology of injury, presence of seizures) and during follow-up (presence of seizures, neurodevelopmental milestones, and behavioral aspects). MRI-scans from the neonatal period, around 3 months and during childhood, if performed, were collected. The available amplitude-integrated EEGs (aEEGs) were analyzed for background pattern and epileptiform activity. Sleep-deprived (nap) EEGs and whole night recordings during follow-up were analyzed for background pattern, presence, location and quantity of epileptiform activity. Results of neurodevelopmental assessments, including screening of cognitive functioning, were collected.

### 2.3. Conventional MRI assessment

MRIs from the neonatal period and around 3 months of age were reassessed by an experienced neonatologist (LSdV) for the extent and location of thalamic injury. MRIs from childhood were assessed by an experienced pediatric neurologist (FEJ) for the same characteristics. Thalamic injury location was scored (anterior/ventral, medial or pulvinar).

### 2.4. Thalamic volume and total brain volume

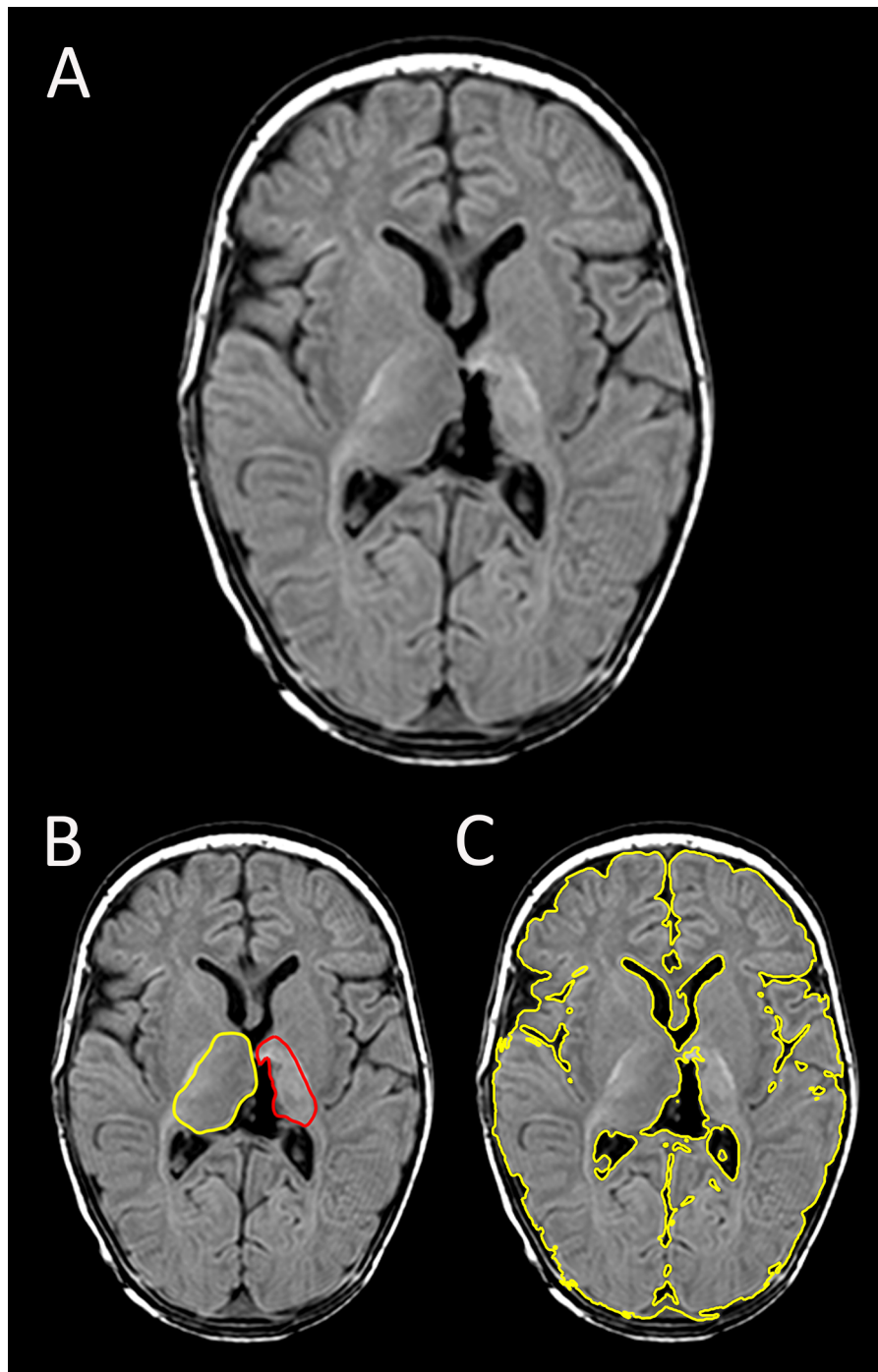
Since MRI scans at 3 months are less influenced by acute injury (i.e. hemorrhage) than neonatal scans, these were used for thalamic and whole brain volumetry. Childhood MRI scans were made at different ages in our population and therefore considered less useful as an early prognostic marker. The software package Mevislab (<https://www.mevislab.de/>) was used to create manual segmentations of the thalamus using T1/T2 images and perform semiautomatic volume-calculation. The thalamus was segmented per slice by one investigator (AFZ) with anatomical atlases as reference. The lateral/ventral border was defined using the posterior limb of the internal capsule as a landmark. The segmentations were checked by 3 investigators (NHCC, BvdM and FEJ) and adjusted where needed. Total brain volume was obtained using FSL (the FMRIB Software Library) for automatic segmentation of the T1/T2 weighted images. The automatically segmented areas were visually inspected, the best segmentation was chosen and manually corrected if necessary. An example of a T1 weighted MRI of an included subject and segmentation of the thalamus and total brain volume is shown in Fig. 1.

### 2.5. Diffusion tensor imaging (DTI)

For patients whose MRI series (at 3 months and at childhood age) included DTI sequences, average bilateral thalamic fractional anisotropy (FA) and mean diffusivity (MD) values were determined. First, artefacts were corrected (e.g. signal drift, subject motion, eddy current induced geometric distortions) and scans were visually inspected for their quality (Vos et al., 2017; Leemans and Jones, 2009; Jones and Leemans, 2011). The scans of sufficient quality were further analyzed per T1-based region of interest (ROI), with the Oishi atlas as a reference template (Oishi et al., 2011). DTI characteristics of the thalamus were calculated using ExploreDTI (Leemans et al., 2009).

### 2.6. Neonatal electroencephalography (EEG)

Two-channel aEEG with corresponding raw EEG data from the neonatal period were collected and analyzed. Background pattern and epileptiform activity during the earliest available 48 h of aEEG were rated through pattern recognition by an experienced neonatologist. Background patterns were scored as continuous normal voltage (CNV, continuous trace, voltage 10–25 (–50)  $\mu$ V), discontinuous normal voltage (DNV, discontinuous trace, voltage predominantly  $> 5\mu$ V), burst-suppression (BS, discontinuous pattern; periods of very low voltage (inactivity) as well as higher amplitude bursts), continuous



**Fig. 1.** Illustrative MRI and segmentation in a 3 months-old patient with left-sided thalamic injury. A. Transversal slice of unprocessed T1 weighted MRI. B. Manual segmentation of the thalamus. C. Automatic segmentation of the total brain volume.

extremely low voltage (CLV, continuous pattern of very low voltage, around or  $< 5 \mu\text{V}$ ), Flat tracing (FT: mainly inactive [isoelectric] trace, with very low voltage  $< 5 \mu\text{V}$ ). Four categories of epileptiform activity were identified: No epileptiform activity (no EA), single seizure (SS:  $< 3$  discharges per 30 min), repetitive seizures (RS:  $\geq 3$  discharges within 30 min), status epilepticus: “sawtooth” pattern.

### 2.7. EEG during follow-up

Because of the known high risk of ESES development after perinatal thalamic injury, children with perinatal thalamic injury are routinely followed-up in our center with periodic sleep-EEGs (either nap EEGs

after sleep-deprivation or whole night registrations). All EEGs were evaluated for the presence of epileptiform activity (spike and wave complexes, spikes or sharp waves) in sleep. The follow-up EEG with the highest spike-wave index (SWI) was used as the “index EEG”, because this was considered to best represent the severity of EEG abnormalities. The age at onset of ESES was variable in this population, thus an SWI assessment at the same age for all patients would not be representative. Also, the first (routine) EEG showing sleep activation of epileptiform activity may just be an early sign of the disease, while later EEGs show the full extent of abnormalities. The “index EEG” was assessed for background pattern, presence and distribution of epileptiform activity during wakefulness, sleep architecture and presence and quantification

of epileptiform activity during sleep (SWI). The SWI was calculated in an epoch of 10 min (600 s) duration, starting 5 min after alpha attenuation or after sleep had clinically commenced. The number of seconds containing epileptiform discharges was divided by the total number of seconds in the epoch (600) and multiplied by 100 to reflect the SWI as a percentage. Classic ESES was defined as an SWI of above 85% and ESES spectrum as an SWI of 50–85%.

## 2.8. Outcome definition

Primary outcome for this study is the occurrence of epilepsy with ESES (-spectrum) abnormalities in the most severely affected EEG during follow-up. Secondary outcome is neurodevelopment as reflected by total Intelligence Quotient (preferred if available) or Developmental Quotient. Before the age of two years developmental quotients were obtained using the Griffiths mental development scales or the Bayley Scales of Infant and Toddler Development. After the age of two years the tests were chosen based on age and abilities of the children and included Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC III), Bayley Scales of Infant and Toddler Development, Griffiths mental development scales as well as the Snijders-Oomen non-verbal intelligence test (SON) in one case. We first performed our analyses with mean IQ/DQ after the age of two years as outcome measure. Subsequently, individual IQ/DQ measurements at all time points before and after the age of two years were used as outcome measure for a linear mixed model analysis.

## 2.9. Statistical analysis

An estimate of the risk of epilepsy with ESES after perinatal thalamic injury, while accounting for a difference in follow-up duration between patients, was provided by creating a Kaplan-Meier Curve for the prospectively followed cohort. Fisher's exact test was used to explore possible associations between thalamic and other injury lateralization and predominant EEG focus of epileptiform activity. The choice of parametric or non-parametric tests was based on the distribution of the data, using parametric tests (*t*-test/ANOVA) if the data did not clearly deviate from normal distribution, whereas for data that was not normally distributed, non-parametric (Mann-Whitney U test, Spearman's rank correlation) tests were used. The thalamic volume of patients who developed ESES (spectrum) was compared to that of patients who did not develop ESES (spectrum) with an independent samples *t*-test. Association between MRI-characteristics and SWI was assessed using Spearman's rank correlation coefficient for continuous and the Mann-Whitney U test for categorical MRI-variables. A possible difference in mean IQ/DQ after two years of age according to the presence of injury in the different thalamic areas was assessed with independent samples *t*-tests. aEEG findings were tested for possible association to mean IQ/DQ after two years by means of a One-way Analysis Of Variance (ANOVA). Complete case univariable and multivariable linear regression analyses were performed with thalamic volume, total brain volume and SWI as possible predictors of mean total IQ/DQ after two years. 95% confidence intervals (95% CIs) were calculated.

To account for differences in baseline intelligence levels between patients, and to include all IQ/DQ measurements despite difference in timing and tests between patients, a linear mixed model was fitted. All IQ/DQ measurements were defined as repeated outcome measures. The intercept was included as a random effect variable and thalamic volume, total brain volume and SWI were included as fixed variables. The covariance matrix model was chosen based on a comparison of the Akaike information criterion (AIC) of the model options in SPSS. The model with the *Factor Analytic: First Order* covariance matrix structure had the lowest AIC and was therefore considered to best fit the dataset.

*P*-values below 0.05 were considered significant. Statistical analysis was conducted using IBM SPSS Statistics Software version 25 by BvdM

with advice and feedback by a clinical epidemiologist (JDJP).

## 2.10. Standard protocol approvals, registrations, and patient consents

The study was approved by the medical ethics committee, who decided that the Dutch Medical Research Involving Human Subjects Act (WMO) did not apply.

## 2.11. Data availability

All anonymized data included in this study will be provided upon reasonable request to the corresponding author.

## 3. Results

### 3.1. Patient characteristics

Twenty-three consecutive patients with perinatal thalamic injury were followed in the UMC Utrecht from the neonatal period onward and could be included in the *prospectively followed (incidence) cohort*. An additional seven patients with perinatal thalamic injury, who were referred during childhood, were included. Patient characteristics of the prospectively followed cohort, the retrospectively added subgroup and the whole cohort are shown in [Table 1](#).

### 3.2. Neurodevelopmental findings during follow-up

A gradual decrease in mean IQ/DQ was seen with age ([Table 1](#)). When comparing IQ/DQ before ESES was first detected (at 24 months) with the first IQ/DQ after ESES (spectrum) diagnosis for patients for whom these data were available at both timepoints ( $n = 18$ ) a decrease from a mean IQ of 89 to 82 ( $p = 0.046$ , average time interval 43 months) was found.

### 3.3. MRI findings ([Table 2](#))

In the total cohort of 30 patients, MR images of sufficient quality for clinical assessment were available from the neonatal period in 24 children, around three months of age in 23, and during childhood in 22 patients. The medial part of the thalamus was most often involved in the injury at the neonatal and three months MRIs, while at the childhood MRI the sequelae of the perinatal thalamic injury were more diffuse ([Table 2](#)). Mean total (bilateral) thalamic volume at three months was 8.11 ml. A small mean increase in FA was seen from age three months into childhood (from 0.240 to 0.278).

### 3.4. Primary findings

#### 3.4.1. Occurrence of ESES (spectrum) abnormalities during follow up

Mean EEG follow-up was 96 months in the *prospectively followed cohort*. Most patients (87%) had a normal background pattern during wakefulness, while in sleep 6 patients had ESES-spectrum abnormalities (26%) and an additional 13 patients showed a classic ESES pattern (57%, [Table 1](#)). The ESES(-spectrum) abnormalities were limited to one hemisphere in 8 cases (42%) and bilateral in 11 cases (58%). There was no significant difference in EEG follow-up between the patients with ESES spectrum abnormalities and those with classic ESES (93 vs 103 months,  $p = 0.62$ ). [Fig. 2](#) shows a Kaplan Meier curve for the occurrence of ESES (spectrum) in the *prospectively followed cohort*.

#### 3.4.2. Imaging predictors for the occurrence of ESES (-spectrum) and for the severity of neurodevelopmental abnormalities

A large majority (19 of 23) of the prospectively followed patients developed ESES (-spectrum) abnormalities during follow-up. The patients who developed ESES, had a lower thalamic volume (mean  $\pm$  sd  $7.8 \pm 1.5$  ml vs.  $9.7 \pm 1.5$  ml,  $p = 0.04$ ). Because of the very small



**Table 1**  
Patient characteristics, clinical, EEG and neuropsychological findings

Neonatal period	All patients (n = 30)	Prospectively followed subgroup (n = 23)	Retrospectively added subgroup (n = 7)
male (%)	17/30 (57%)	15/23 (65%)	2/7 (29%)
gestational age: mean (± sd)	39 (± 2,5) weeks	39 (± 2,5) weeks	38 (± 2,7) weeks
pregnancy complications	12/29 (41%)	11/23 (48%)	1/6 (17%)
delivery complications	11/28 (39%)	11/23 (48%)	0/5 (0%)
birth weight: mean (± sd)	3148 (± 859) grams	3151 (± 877) grams	3123 (± 866) grams
Apgar score at 1/5/10 min:	7/9/9	7/9/9	7/9/-
mean	8/9/10	8/9/10	8/9/-
median	4/5/6	4/5/6	4/8/-
min	9/10/10	9/10/10	8/10/-
max			
etiology:	20	17	3
sinus thrombosis	5	3	2
arterial ischemic	2	2	0
isolated hemorrhage	2	1	1
infectious	1	-	1
venous malformation			
neonatal convulsions	24/30 (80%)	19/23 (83%)	5/7 (71%)
aEEG findings:	n = 15	n = 15	N/A
PMA at aEEG: mean (± sd)	40,6 (± 1,4) weeks	40,6 (± 1,4) weeks	
background*: CNV/DNV/BS/CLV/FT	3/11/0/0/1	3/11/0/0/1	
epileptic activity	13 (87%)	13 (87%)	
follow-up during childhood			
duration of EEG follow-up: mean (± sd)	95 (± 40) months	96 (± 40) months	93 (± 42)
seizures:	12 (40%)	10 (43%)	2 (29%)
focal	4 (13%)	3 (13%)	1 (14%)
generalized	5 (17%)	2 (9%)	3 (43%)
both	9 (30%)	8 (35%)	1 (14%)
none			
age at seizure onset: mean (± sd)	43 (± 28) months	38 (± 21) months	54 (± 42) months
EEG findings:	22 (73%)	20 (87%)	2 (29%)
wake: normal background	3 (10%)	3 (13%)	0 (0%)
sleep: no SIEA	1 (3%)	1 (4%)	0 (0%)
SIEA	8 (27%)	6 (26%)	2 (29%)
ESES-spectrum	18 (60%)	13 (57%)	5 (71%)
classic ESES			
Highest SWI in sleep:	78 (± 30)%	75 (± 33)%	91 (± 12)%
mean (± sd)	91%	89%	98%
median	0–100%	0–100%	70 - 100
range			
Number of anti-epileptic drugs used: mean (± sd)	3 (± 3)	3 (± 3)	4 (± 3)
Neurodevelopment before documented ESES (spectrum):	22 (73%)	18 (78%)	4 (57%)
normal	4 (13%)	3 (13%)	1 (14%)
intellectual impairment (IQ/DQ 70–85)	4 (13%)	2 (9%)	2 (29%)
intellectual disability (IQ/DQ < 70)			
Dominant neurodevelopmental abnormalities during follow-up/after ESES	13 (43%)	9 (39%)	4 (57%)
onset:	5 (17%)	3 (13%)	2 (29%)
global cognitive impairment	1 (3%)	1 (4%)	0 (0%)
language impairment	11 (37%)	10 (44%)	1 (14%)
behavioral disorder	5 (17%)	2 (9%)	3 (43%)
none	9 (30%)	6 (26%)	3 (43%)
Severity of ESES related impairment:	5 (17%)	5 (22%)	0 (0%)
regression	11 (37%)	10 (44%)	1 (14%)
arrest			
delay			
none			
Total IQ/DQ during follow-up (mean ± sd) at	102 (± 14), n = 15	102 (± 14), n = 15	N/A
~6 months	93 (± 20), n = 23	94 (± 18), n = 22	55, n = 1
~12 months	90 (± 15), n = 22	92 (± 13), n = 21	55, n = 1
~24 months	86 (± 19), n = 16	89 (± 18), n = 15	55, n = 1
~2–5 years	82 (± 17), n = 16	89 (± 17), n = 12	71, n = 4
~5–8 years	66 (± 16), n = 10	73 (± 17), n = 6	56, n = 4
~8–13 years			

sd: standard deviation aEEG: amplitude-integrated EEG PMA: post-menstrual age.

CNV: continuous normal voltage DNV: discontinuous normal voltage.

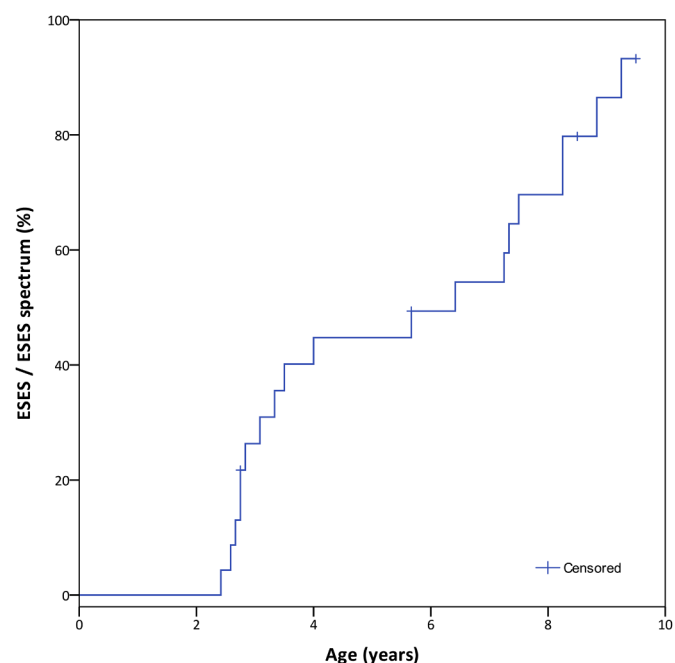
BS: burst-suppression CLV: continuous extremely low voltage FT: flat trace N/A: Not available.

SWI = spike-wave index SIEA = sleep induced epileptiform activity.

\* Background is defined as worst background pattern and might have been influenced by medication. The patient with a FT background pattern was administered clonazepam and phenobarbital during aEEG registration. After six hours of severe aEEG depression his background showed marked improvement.

**Table 2**  
MRI findings.

	Neonatal (n = 24)	~3 months (n = 23)	Childhood (n = 22)
Lateralization thalamic injury	7 (29%)	8 (35%)	6 (27%)
<i>right sided</i>	9 (38%)	11 (48%)	10 (46%)
<i>left sided</i>	7 (29%)	4 (17%)	6 (27%)
<i>bilateral</i>	1 (4%)		
<i>none visible</i>			
Lateralization other MRI abnormalities	1 (4%)	4 (17%)	1 (5%)
<i>right sided</i>	0 (0%)	5 (22%)	3 (14%)
<i>left sided</i>	23 (96%)	11 (48%)	16 (73%)
<i>bilateral</i>		3 (13%)	2 (9%)
<i>none visible</i>			
Thalamic areas involved (multiple areas can be involved)	18 (75%)	7 (30%)	20 (91%)
<i>anterior/ventral</i>	20 (83%)	20 (87%)	18 (82%)
<i>medial</i>	14 (58%)	8 (35%)	19 (86%)
<i>pulvinar</i>			
Thalamic volume (T1/T2, ml): mean (± sd)		4.32 (± 1.05)	
<i>right</i>		3.79 (± 1.45)	
<i>left</i>		8.11 (± 1.67)	
<i>total</i>		(n = 21)	
Total brain volume (T1/T2, ml): mean (± sd)		526.45 (± 88.99)	
Thalamic fractional anisotropy (DTI)		0.242	0.282
<i>right</i>		0.239	0.273
<i>left</i>		0.240	0.278
<i>mean</i>		(n = 11)	(n = 9)
Thalamic mean diffusivity (DTI, mm <sup>2</sup> /s)		0.0013	0.0014
<i>right</i>		0.0014	0.0016
<i>left</i>		0.0014	0.0015
<i>mean</i>		(n = 11)	(n = 9)



**Fig. 2.** Kaplan-Meier curve for ESES or ESES spectrum in the incidence cohort (n = 23). The percentage of patients with perinatal thalamic injury with ESES/ESES spectrum is related to age.

group of patients (n = 4) who did not develop ESES (spectrum) abnormalities, we considered statistical power too small to compare other characteristics between the two groups.

**Table 3**  
Correlation of MRI characteristics and SWI/IQ during follow-up.

	SWI (%)		IQ	
	<i>rho</i>	<i>p</i>	<i>r</i>	<i>p</i>
volumetric measurements at ~3 months MRI (n = 21)				
total thalamic volume (ml)	-0.42	0.06	0.74	0.001
<i>unilateral cases*: volume of affected side (ml)</i>	-0.39	0.11	0.38	0.17
<i>unilateral cases*: volume of contralateral side (ml)</i>	-0.34	0.16	0.84	<0.001
total brain volume (ml)	-0.23	0.32	0.64	0.005
DTI characteristics				
~3 months DTI (n = 11)				
thalamic fractional anisotropy (FA)	0.58	0.06	0.03	0.93
thalamic mean diffusivity (MD)	-0.07	0.82	0.42	0.26
childhood DTI (n = 9)				
thalamic fractional anisotropy (FA)	-0.81	0.008	0.76	0.03
thalamic mean diffusivity (MD)	0.72	0.03	-0.81	0.02

*rho* = Spearman's *rho* *r* = Pearson's correlation coefficient.

\* n = 18 cases with unilateral thalamic injury based visual inspection of the ~3 months MRI.

Larger thalamic volume and larger total brain volume, measured on three months MRI, were correlated to higher mean IQ/DQ after the age of 2 years ( $r = 0.74, p = 0.001$  and  $r = 0.64, p = 0.005$ , Table 3 and supplementary Figure 1). Injury involving the anterior/ventral portion of the thalamus was the only of the three predefined areas that was associated with mean IQ/DQ after 2 years of age (mean IQ/DQ 72 for those with vs. 89 for those without anterior/ventral injury,  $p = 0.04, n = 19$ ). In a subgroup of patients with unilateral thalamic injury, according to visual inspection of the 3 months MRI (n = 18), the volume of the affected thalamic hemisphere was not correlated with, while the volume of the contralateral thalamic hemisphere was positively correlated with mean IQ/DQ after the age of 2 years ( $r = 0.38, p = 0.17$  and  $r = 0.84, p < 0.001$ , Table 3).

Multivariable linear regression analysis revealed that mean IQ/DQ after the age of two years was correlated with thalamic volume ( $\beta$  6.4 [95% CI 0.65 – 12.1]), but no longer with total brain volume ( $\beta$  0.05 [95% CI -0.06 – 0.16]) and SWI ( $\beta$  0.08 [95% CI -0.12 – 0.27]). Thus, corrected for total brain volume and SWI, a 1 ml higher thalamic volume was associated with an increase of 6.4 IQ points in this analysis.

With a linear mixed model we found that thalamic volume was an independent predictor of IQ/DQ (univariable coefficient 7.2 [95% CI 5.3 – 9.1], multivariable coefficient 9.6 [95% CI 5.9 – 13.3]), while total brain volume and SWI were not significantly correlated with IQ/DQ (Table 4). This means that, corrected for total brain volume and SWI and accounting for repeated measures within patients, a 1 ml higher thalamic volume was associated with a 9.6 points higher IQ.

### 3.4.3. Exploratory analysis of DTI characteristics and neurodevelopment during follow-up

Thalamic DTI characteristics at three months were not predictive for mean IQ/DQ after the age of 2 years. Childhood MRI DTI characteristics, however, were correlated with mean IQ/DQ after the age of two years: higher FA and lower MD predicted higher IQ ( $r = 0.76, p = 0.03$  and  $r = -0.81, p = 0.02$  respectively, Table 3).

## 3.5. Additional findings

### 3.5.1. Correlation of MRI characteristics to epileptiform activity during follow-up

9 of 11 patients with unilateral thalamic injury and a lateralized EEG focus in sleep had their predominant EEG focus on the same side as their thalamic injury focus. Nonetheless, lateralization of thalamic injury ( $p = 0.09$ ), or lateralization of other MRI abnormalities ( $p = 0.99$ )

**Table 4**  
Possible predictors of cognitive function during follow-up.

Linear regression analysis of mean IQ outcome, at age > 2 years		
	Univariable $\beta$ (95% CI)	Multivariable $\beta$ (95% CI)
thalamic volume (ml)	7.3 (3.7–11.0)	6.4 (0.6–12.1)
total brain volume (ml)	0.13 (0.04–0.21)	0.05 (–0.06–0.16)
SWI (%)	–0.19 (–0.42–0.04)	0.08 (–0.12–0.27)
Mixed linear model with DQ/IQ measurements as repeated measures		
	Univariable coefficient (95% CI)	Multivariable coefficient (95% CI)
thalamic volume (ml)	7.2 (5.3–9.1)	9.6 (5.9–13.3)
total brain volume (ml)	0.07 (–0.02–0.15)	–0.06 (–0.13–0.01)
SWI (%)	–0.18 (–0.38–0.02)	0.02 (–0.12–0.16)

DQ: developmental quotient, IQ: Intelligence Quotient.

SWI: Spike-wave index.

were not correlated to the predominant localization of epileptiform activity in sleep. There was no association between the affected thalamic areas at the three months MRI and SWI during follow-up. Thalamic volume at the three months MRI showed a trend towards correlation, while total brain volume did not show a correlation with SWI during follow-up ( $\rho = -0.42$ ;  $p = 0.06$  and  $\rho = -0.23$ ;  $p = 0.32$ ,  $n = 21$ ). DTI characteristics at three months ( $n = 11$ ) were not correlated to SWI either ( $\rho = 0.58$ ;  $p = 0.06$  for FA and  $\rho = -0.07$ ;  $p = 0.82$  for MD), while DTI characteristics at the childhood MRI ( $n = 9$ ) were strongly correlated to SWI: a higher thalamic FA was correlated to lower SWI ( $\rho = -0.81$ ,  $p = 0.008$ , Table 3) and higher thalamic MD was correlated to higher SWI ( $\rho = 0.72$ ,  $p = 0.03$ , Table 3).

### 3.5.2. Correlation of aEEG, MRI characteristics and SWI to neurodevelopmental findings during follow-up

The aEEG background pattern and presence/severity of epileptiform activity in the neonatal period were not correlated to mean IQ/DQ after two years of age ( $p = 0.43$  and  $p = 0.62$ ,  $n = 14$  with available aEEG from the neonatal period and neurodevelopmental follow-up after the age of 2 years).

## 4. Discussion

In this study, we show that (1) the majority of patients with perinatal thalamic injury eventually develop epilepsy with classic ESES (SWI > 85%) or ESES spectrum (SWI 50–85%), (2) Patients with perinatal thalamic volume who develop ESES(-spectrum) during follow-up had a lower thalamic volume at 3 months as compared to patients who did not develop ESES(-spectrum). Furthermore, higher residual thalamic volume at three months of age correlates with higher IQ/DQ at follow-up - also after correction for total brain volume and spike wave index - and (3) thalamic DTI indices during childhood correlate with the severity of epileptiform activity in sleep and with cognitive functioning.

The Kaplan Meier curve of our incidence cohort suggests that more than 90% of children with perinatal thalamic injury develop epilepsy with ESES spectrum abnormalities during follow-up. Previous studies also suggested a strong link between thalamic injury and ESES spectrum abnormalities (Guzzetta et al., 2005; Kersbergen et al., 2013). The current study is the first to confirm this in a prospectively followed cohort with long-term follow-up. As almost all patients had ESES during follow-up, we were unable to find predictors of the occurrence of ESES within the population of children with thalamic injury. Several possible mechanisms behind the occurrence of ESES in children with thalamic abnormalities have been proposed. The thalamus has the capacity to generate rhythmic oscillations (e.g. sleep spindles) in a thalamocortical circuit that is activated during sleep. These oscillations are thought to

result from balanced activity between thalamic excitatory neurons and  $\gamma$ -aminobutyric acid (GABA)ergic inhibitory neurons (Steriade, 2005). Loss or dysfunction of thalamic inhibitory neurons may lead to a pathologic derangement of these oscillations during sleep, as reflected by rhythmic spike and wave discharges (Siniatchkin et al., 2010; Beenhakker and Huguenard, 2009; Agarwal et al., 2016). As an additional mechanism, a recent study suggested that loss of thalamic control of plasticity of part of the cortex (i.e. incomplete loss of thalamocortical connectivity) leads to a pathological “augmentation response” and thereby a hyperexcitable cortical network (Leal et al., 2018).

We investigated whether neurodevelopment can be predicted by the residual thalamic volume and found a strongly significant correlation: higher total thalamic volume at three months of age predicted higher IQ/DQ during follow-up. In cases with unilateral thalamic injury based on inspection of the three months MRI by the clinician, the volume of the contralateral thalamus was significantly correlated to mean IQ/DQ during follow-up while the ipsilateral thalamus was not. This suggests that the cognitive performance depends mainly on the least affected side. It could be that, although normal on visual inspection, more subtle changes in structure and function of the contralateral thalamic hemisphere are also present and that volume of the contralateral thalamic hemisphere is indicative of the compensatory capabilities.

Previous studies in both adults and children also found a correlation of thalamic volume and thalamocortical connections with aspects of cognitive functioning (Hughes et al., 2012; Ball et al., 2015). Recent studies have suggested that the thalamus has an important role in sustaining attention, not only by filtering information to and between cortical regions, but also by enhancing the functional connectivity of relevant cortical areas (Halassa and Kastner, 2017). We hypothesized that, in addition to volume loss, altered structural organization of the thalamus could explain the cognitive deficits that are seen in children with epilepsy with ESES. By analyzing DTI characteristics of the thalamus, we explored this hypothesis. Although we did not find such a correlation when DTI measures were studied at the age of three months, higher thalamic FA and lower MD on DTI scans acquired during childhood were associated with higher IQ/DQ, suggesting that thalamic microstructure, as well as its volume, is important for neurodevelopment. Also, we found that higher FA and lower MD on later DTI scans were associated with lower SWI, which may reflect that more organized thalamic microstructure is associated with less epileptiform activity in sleep.

We found that a higher percentage of epileptiform activity, expressed as the spike-wave index, correlates to lower IQ after perinatal thalamic injury. ESES may be a factor that influences cognitive functioning in addition to the impact of the thalamic injury itself, or it could merely be a marker of severity of thalamic injury. Previous studies suggested that ESES itself contributes to cognitive deficits (Scholtes et al., 2005; Pera et al., 2013; Tassinari and Rubboli, 2006) and that

improvement of cognitive functioning can be expected if epileptiform activity is reduced with treatment (van den Munckhof et al., 2018). However, in these papers, wider populations were studied, including children in whom an underlying etiology was not detected. Future studies comparing patients with ESES after thalamic injury and patients with ESES of non-structural etiology (although this also is a heterogeneous group) may further elucidate whether the thalamic injury or the ESES is the main determinant of long-term neurodevelopment. In our multivariable analysis we did not find a significant correlation of SWI with IQ. A possible explanation is that, for each patient, we included the EEG with the highest SWI and did not consider that in some cases the epileptiform activity was reduced or disappeared with treatment.

Our study is the first to quantitatively assess the risk of epilepsy with ESES after thalamic injury in a prospectively followed cohort and combine multiple modalities (MR volumetry, DTI and EEG) as well as repeated clinical/neuropsychological assessments to reveal predictors of cognitive functioning.

Our results have to be interpreted with care. First, the relatively small and somewhat heterogeneous study population (inherent to the rarity of perinatal thalamic injury) inevitably results in some uncertainty regarding the cumulative incidence of epilepsy with ESES after thalamic injury. Second, although MRI acquisition in our center was done according to a standard schedule, MRI protocols changed during the period of conduct of our study, which results in variability of available imaging data. Especially our analysis of DTI characteristics should be seen as explorative as these sequences were available in a minority of patients. Our DTI data were of insufficient quality and quantity for reliable analysis of thalamocortical tracts and this would be an interesting subject to address in a future study. Although developmental screening in the first two years was done according to a standard protocol, follow-up afterwards with full neuropsychological assessment was performed at variable time points and may have been selective (patients with learning problems could have been tested more often). Lastly, the use of a multivariable mixed model analysis allowed the use of multiple TIQ measurements per patient and adjusts for the fact that each patient has his/her own “baseline” total IQ. However, using this multivariable mixed model in our relatively small study population, may have led to overfitting and could limit the generalizability of our results.

The results of our study implicate that clinicians treating children with perinatal thalamic injury should be aware of the risk of epilepsy with ESES. We recommend careful follow-up with assessment of cognitive functioning and serial sleep EEGs after the age of two years in these children. Parents should be made aware that a cognitive or behavioral deterioration of their child needs prompt evaluation. In case of ESES accompanied by a cognitive decline, treatment should be initiated soon, because early treatment of epilepsy with ESES can improve neurodevelopmental outcome (Van Den Munckhof et al., 2015; Pera et al., 2013; van den Munckhof et al., 2018; Maltoni et al., 2016).

In conclusion, perinatal thalamic injury is often followed by electrical status epilepticus in sleep in children after the age of two years. Cognitive performance of these children has a strong correlation with residual thalamic volume. The cognitive deficits in these patients may also be explained by abnormal structural organization of the thalamus as reflected by DTI characteristics. Future studies may elucidate whether loss of physiological thalamocortical connections explains these cognitive deficits.

#### Ethical publication statement

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

#### Disclosures

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

#### CRediT authorship contribution statement

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.nicl.2020.102227](https://doi.org/10.1016/j.nicl.2020.102227).

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