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Abbreviations: ASM = Antiseizure medication; IQ = intelligence quotient; IQR = interquartile range; NPA = neuropsychological assessment; PIQ = performance IQ; RC = regression coefficient; TIQ = total IQ; VIQ = verbal IQ.

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Declarations

Previous publication of study results: Preliminary results of this study were presented by poster at the European Congress of Epileptology in 2018.

Availability of data and material: Anonymized data generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Statistical code will be shared with any qualified investigator by emailing the corresponding author.

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.

Consent to participate: The researcher approached patients with an active treatment relation at the University Medical Center in Utrecht, the Netherlands, to obtain informed consent. Patients who previously objected to being part of scientific research were excluded.

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Abstract

Objective Antiseizure medication may have long-term effects on the neurodevelopment of children. We aimed to investigate the association between cumulative antiseizure medication load and intelligence quotient (IQ) in relation to brain volume and cortical thickness.

Methods Retrospective analysis of children with focal epilepsy who underwent neuropsychological assessment and MRI between the ages of 5-12 years in a tertiary epilepsy center. Cumulative medication load was presented in medication years. We studied the association between total medication load and IQ with multivariable linear regression, corrected for epilepsy-related confounders: age at first treatment, etiology, maximum seizure frequency, duration of active epilepsy, history of secondary generalized seizures, history of status epilepticus, and the number of antiseizure medications used at time of neuropsychological assessment.

Results We included 59 children, median medication load was 5.3 medication-years (interquartile range: 2.0 – 11.1), mean total IQ (± standard deviation) 77.4±18.9. A significant negative relation between medication load and total IQ was found with a decrease of 1.2 IQ-points per medication-year (95% confidence interval (CI): -2.0 to -0.3) after correcting for confounders. Medication load was not significantly associated with brain volume or cortical thickness, nor were the latter with IQ.

Significance Higher cumulative medication load is associated with lower total IQ after adjusting for epilepsy-related confounders. We found no evidence to support the hypothesis that the medication-related IQ decrease was mediated by volumetric brain changes. However, these results should be interpreted with caution, and prospective, longitudinal confirmation of these findings is required. Lastly, it should be stressed that effective seizure prevention often outweighs the potential negative effects of antiseizure medication.

Key words: cognition, intelligence quotient, neurodevelopment, structural connectivity

Key point box:

- This study provides new insight into long-term cumulative effects of antiseizure medication on intelligence in children with epilepsy while correcting for the effects of epilepsy itself.
- Higher antiseizure medication load is associated with lower total IQ.
- No evidence for underlying changes in brain thickness and volume.

Introduction

Epilepsy is one of the most common brain disorders in children, with a prevalence of approximately 1% of all children[1]. A major issue in children with epilepsy is cognitive comorbidity. The underlying pathology [2,3] and epilepsy-related factors [4,5] may cause this comorbidity, but an additional reason for concern is the possible side effects of antiseizure medication (ASM).

Many studies have demonstrated that children who are using ASM experience cognitive side effects [6-10]. These studies, however, did not look at any potential long-term effects. The only knowledge we have on potentially harmful effects of ASM use on neural development comes from two fields of research: rodent studies [9] and studies on cognitive outcome after prenatal exposure of children to their mothers' ASM. ASM may affect the unborn child's brain development during pregnancy and increase the risk of intellectual disability, language impairment, psychomotor decline, and autism spectrum disorders [9,11-14].

Neurodevelopment, however, does not stop after birth. Critical processes take place between the ages of one and six years, such as maturation of cortical structures and establishing their connectivity [15]. Furthermore, dendrite growth, synaptogenesis, and myelination, amongst others, continue until adulthood [16]. Only one study has shown potential long-term effects of ASM on eventual intelligence quotient (IQ), which was a trial using phenobarbital in children with febrile seizures [17,18]. However, this is not informative for current practice, as this drug is now rarely prescribed beyond the neonatal age. Because the mechanism of action of ASM includes many pathways that are also important in the brain's developmental processes, we hypothesized that the use of ASM early in life can affect brain development and eventual intellectual functioning.

We tested this hypothesis with an assessment of the long-term effect of exposure to ASM on IQ as a broad measure of neurodevelopment. The secondary aim was to investigate whether the relation between ASM and IQ was mediated by cortical thickness and brain volume measures.

Methods

Study population

In this retrospective cohort study, data were obtained from children with epilepsy [19] evaluated and followed at our outpatient child neurology clinic, our first seizure clinic, and from those who were evaluated for epilepsy surgery between 2005 and 2017. Children were included when they had focal epilepsy according to the International League Against Epilepsy classification [20]. Additional inclusion criteria were the availability of a neuropsychological assessment (NPA) during or after medication treatment and a magnetic resonance brain (MRI) scan for measuring cortical thickness and volumes (T1-weighed 3D MRI at 1.5 or 3.0 Tesla). Both NPA and MRI had to be performed between the age of five and twelve years. Children with NPA or MRI below the age of five were excluded because of the difficulty of reliable automatic segmentation of MRI due to poor grey-white differentiation and shape differences to adult templates in immature brains [21]. Age at first treatment could have been before the age of 5 years. The maximum age of twelve years was chosen to limit the age span and reduce study population heterogeneity. To study the effect of ASM on the cortex, only children with focal epilepsy were included, confined to a single hemisphere, as based on semiology, (inter)ictal EEG findings, and in case of structural etiologies, the exclusion of contralateral MRI-lesions.

Furthermore, patients were excluded when there was a risk of a diffusely affected brain, for instance, patients with a history of generalized epilepsy, tuberous sclerosis complex, mitochondrial or another metabolic disease, or children who had suffered from epileptic encephalopathies at some point during their disease (*Box 1*). Similarly, patients who have epilepsy requiring hemispherectomy were excluded. Patients with a history of oral steroid treatment or thiopental coma were excluded from analysis as these interventions may influence total brain volume. Lastly, patients were excluded when they underwent epilepsy surgery before NPA and acquisition of MRI, as epilepsy surgery itself impacts cognition [5].

The Dutch Medical Research Involving Human Subjects Act did not apply, as confirmed by the Ethical Committee of the University Medical Center in Utrecht. The researcher approached patients with an active treatment relation at this center to obtain informed consent. Patients who previously objected to being part of scientific research were excluded.

Medication load calculations

Cumulative medication load was calculated by adding the years each antiseizure drug was taken until the NPA. Since the effect of long-term exposure to ASM was our primary interest, rescue medication for acute seizures was not considered in this calculation. Medication load is defined in units of medication years, where one medication year corresponds to one antiseizure drug being taken for one year. As an example, when a child used both valproic acid and levetiracetam for one year during the timespan preceding NPA, the medication load was two medication years. Data were also collected regarding the number of ASMs taken at the time of NPA and MRI as potential confounders.

Brain structure measurements

The MRI sequences were visually inspected for quality, and scans with excessive artifact precluding automated processing were excluded. Scans were segmented and parcellated using Freesurfer Version 5.3.0 [22]. Cortical thickness [23] was calculated at each surface vertex as the distance from the grey-white boundary to the cortical surface using the regions of the Desikan-Killiany atlas [24]. All segmentations and parcellations were manually checked for accuracy. We made manual adjustments to registration, parcellation and segmentation if necessary. Only measurements from the hemisphere from which seizures did not arise were considered. The mean cortical thickness of the entire healthy hemisphere, contralateral to the seizure focus, and several specified cortical regions were analyzed. The precentral gyrus, caudal middle frontal gyrus, paracentral gyrus, and superior frontal gyrus were specifically investigated because cortical thickness in these regions has been reported to be most affected in people with epilepsy [25]. Cerebral volume changes were studied, investigating total hemisphere volume and the ratios between white matter volume / total hemisphere volume, and cerebellar volume / total hemisphere volume. Volumes of thalamus, pallidum and putamen were also analyzed, following the findings described by Whelan and colleagues [25]. Regions analyzed are displayed in *Figure 1*.

Endpoints of interest

The primary endpoint was IQ, which was assessed in children who underwent neuropsychological assessment for clinical reasons at the treating physician's discretion. Whenever multiple NPAs were available, results from the latest assessment were included. A clinical child neuropsychologist carried out all NPAs. Each NPA resulted in standardized scores for total intelligence quotient (TIQ), verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ).

Data collection and analysis

Data were obtained from patient records and consisted of general patient characteristics, epilepsy characteristics, results of structural MRI as concluded by an epilepsy-dedicated neuroradiologist, detailed information on drug therapy, and results from NPA. Multiple factors influence cognitive epilepsy outcome [4,5]: etiology, maximum seizure frequency, duration of active epilepsy, age at onset of antiseizure treatment, history of secondary generalized seizures, history of status epilepticus requiring hospitalization and the number of ASMs used during NPA. Since these factors may also influence the medication load, they were predefined as potential confounders. Definitions of the confounders are listed in *Box 1*.

We tested the relation between medication load and IQ univariably for the primary endpoint using linear regression to get a crude estimate of the association. Next, multivariable regression analysis was performed by adding a propensity score, computed using all possible confounders, to the analysis to obtain an adjusted regression coefficient. Children with IQ<70 are considered to have cognitive impairment; as a sensitivity analysis, all patients with an IQ < 70 were excluded and the analysis was repeated. Secondly, to assess the hypothesis that the effect of medication load on IQ was mediated by changes in cortical structures or brain volume, a mediation analysis [26] was performed in three steps as visualized in *Figure S1*.

Statistical analysis was performed using SPSS Statistics (Version 25). For the primary analyses, $p < 0.05$ was considered statistically significant. A Bonferroni correction for multiple testing was applied for the secondary analyses, resulting in an alpha level of $0.05/11 = 0.0045$. Since sample size was limited, all multivariable regression analyses included propensity scores computed of all predefined possible confounders.

Results

We screened 1658 children for eligibility, and finally included 59 patients (*Figure S2*). Most frequent reasons for exclusion were no diagnosis of epilepsy (n=885), no MRI acquired in our center (n=305), types of epilepsy other than focal (n=148), and no available MRI and NPA between the age of 5-12 years (n=51). Baseline characteristics of the study participants are presented in *Table 1*. Median medication load (interquartile range (IQR)) was 5.3 medication-years (2.0 – 11.1) and the median duration of active epilepsy was 4.1 years (1.9 – 6.7). The timing of the MRI and NPA was closely related, with a median (IQR) duration of active epilepsy until NPA being 4.1 years (1.7 – 6.7), and until MRI 4.1 years (1.9 – 6.7). The most commonly used drugs were valproic acid (57 patients), clobazam (38 patients) and carbamazepine (37 patients) (*Table S1*). Mean (±SD) IQ scores were TIQ 77.4 (±18.9), VIQ 83.9 (±18.2), and PIQ 80.3 (±15.0).

An increase in medication load was associated with a decrease in TIQ. This association was significant in both the crude linear regression (regression coefficient (RC) -1.7 per medication-year; 95% confidence interval (CI) -2.2 to -1.1) and the adjusted model (RC -1.2; CI -2.0 to -0.3) (*Table 2*). Crude analyses for both VIQ and PIQ showed that an increase in medication load was significantly associated with a decrease in VIQ or PIQ (*Figure 2*); (VIQ RC -1.5; CI -2.2 to -0.8; PIQ RC -1.2; CI -1.9 to -0.5). This association remained marginally significant for only PIQ after adjustment for potential epilepsy-related confounders (*Table 2*). Sensitivity analyses for patients with TIQ≥70 revealed a significant association for TIQ and PIQ in multivariable regression analyses (TIQ RC -1.6; CI -2.9 to -0.3; PIQ RC -2.2; CI -3.5 to -0.9), although not for VIQ (RC -1.0; CI -2.5 to 0.7) (*Table S2*). *Table S3* breaks down the effect of ASM load into medication load during monotherapy and medication load during polytherapy. The adjusted effects are similar to the main effects described in *Table 2*, with a significant

correlation between drug load and TIQ, VIQ and PIQ in children with monotherapy, and a significant correlation between drug load and TIQ in case of polytherapy.

Linear regression analyses between medication load and brain thickness and volume measures did not reveal a significant association in crude and adjusted models with the Bonferroni corrected alpha-level of 0.0045 (*Table 3*). Additionally, no significant association was found between cortical thickness and volumes of individual brain structures and TIQ, VIQ and PIQ scores (*Table 4*). The third step of the mediation analysis (*Figure S1*) was not executed because the first two steps did not show any significant association between medication load and brain structure nor between brain structure and IQ.

Interestingly, in the adjusted models, thalamus volume tended to correlate with IQ, only becoming significant for PIQ, after adjustment for other factors: RC 7.6 IQ points per mm^3 volume increase (CI 1.4 to 13.7, p = 0.02) (*Table 4*). However, this variable did not cross the Bonferroni-corrected alpha-level of 0.0045 and should therefore be considered non-significant.

Discussion

The main finding of this study is that higher cumulative ASM load is associated with lower eventual TIQ in children. This result remained significant after adjustment for epilepsy-related confounders, including the use of ASM at time of neuropsychological assessment, suggesting that the observed association is explained by the cumulative effect of previously used medication itself. A similar, only marginally significant association was observed for PIQ. No significant association was found between medication load and cortical thickness or brain volume of the unaffected hemisphere, nor between cortical thickness or brain volume of the unaffected hemisphere and IQ. To illustrate the clinical implication of these results, the

median medication load in the study population was 5.3 medication years, which would translate to an average TIQ reduction of 6.1 points (CI -10.7 to -1.6), which is not negligible in children. Future studies investigating whether there are any associations amongst ASM, IQ and subcortical volumes [27] and or brain networks [28] in children with focal epilepsy would be of interest.

Whereas most studies have focused on direct cognitive side effects of ASM during use [6-10], the long-term effects of ASM exposure on cognitive function remain largely unknown. Farwell and colleagues studied the long-term effects of ASM on IQ in children in a relatively healthy cohort of children with febrile seizures [17]. In this trial 217 patients with febrile seizures, aged 8 to 36 months, were randomized to a phenobarbital or placebo treatment arm and followed for two years. At the end of the trial, the average IQ score in the phenobarbital arm was 8.4 points lower than in the placebo group (CI -13.3 to -3.5). After discontinuation of the trial medication, the difference was still 5.2 IQ points (CI -10.5 to 0.04), and 3-5 years after the trial the children from the phenobarbital group scored lower on a Wide Range Achievement Test [18]. However, there was no significant difference in average group IQ anymore. Both the Farwell trial and our study suggest long-term effects of ASM on cognition, although both have limitations. In the case of the Farwell trial, results are based on intention-to-treat analyses, and many participants stopped trial medication or were lost to follow-up. Also, currently phenobarbital is not prescribed as a standard treatment against epilepsy beyond the neonatal period.

Recently, the ENIGMA-epilepsy consortium investigated structural brain abnormalities in epilepsy patients and healthy controls [25]. Compared to healthy controls, significantly smaller volumes of the thalamus, hippocampus, and pallidum of people with epilepsy were shown, and reduced cortical thickness was found across seven regions bilaterally. In our study, which did

not include control subjects, we could not find an association between structural changes in these regions and medication load, nor with IQ. Because our study did not find mediation of the association between medication load and IQ by changes in brain volume or cortical thickness, the pathophysiological mechanism behind the influence of ASM on IQ remains unclear. Although the absence of gross volumetric MRI changes is reassuring, it certainly does not exclude subtle changes in cortical microstructure and connectivity, nor subcortical changes. Neurogenesis, apoptosis, synaptogenesis and pruning are all relevant processes for neurodevelopment [16,29]. Disturbing these developmental processes might account for cognitive deficits in humans pre- or postnatally exposed to ASM [29]. The hypothesis is that these disturbances are related to decreased neuronal activity during development, since all antiseizure drugs share this effect [30]. Animal studies have given some insight into the possible neurotoxic effect of ASM. In rodent studies, it has been shown that some ASM trigger widespread apoptotic neurodegeneration throughout the developing brain when administered during the period of rapid brain growth [30].

Furthermore, it was suggested that neurotransmitters could modulate the proliferation of neural stem cells, neuroblasts and glioblasts, regulate migration and induce differentiation [31-34]. In this way, pharmacological agents interfere with neurotransmission. Similarly, ASM may cause permanent defects in the central nervous system. These findings in animal studies suggest a potential influence of ASM on neurodevelopment in humans. The results of the current study seem to support the theories above.

A strength of this study is that it provides new insight into long-term cumulative effects of ASM on intelligence, as previous research mostly focused on ASM's short-term adverse cognitive effects. Second, the effect was studied while adjusting for known confounders,

including the number of ASMs used at the time of NPA to exclude the ASM's acute side effects. Finally, the amount of missing data were limited, despite the retrospective study design.

A conclusion regarding a causal relationship between medication load and IQ can however not be drawn, as this study has several limitations. The study population consisted of a selected group of children, since a patient was only included when both NPA results and 3D T1 MRI were available. However, NPA will usually be performed in children with a suspicion of cognitive deficits (following Dutch Guidelines [35]) or with severe epilepsy, possibly excluding less affected children from the study, leading to potential selection bias. The finding that general IQ scores were remarkably low in our cohort supports this theory. The lower IQ scores were not explained by the etiology of epilepsy, which was most frequently structural, but it is a potential indication of a selected cohort. This could have resulted in an overestimation of the relationship between medication load and IQ. However, subgroup analysis of patients with TIQ≥70 still revealed a significant, negative association for medication load and TIQ, supporting the claims of the main analysis.

As NPAs before start of drug treatment were unavailable, no longitudinal comparison at the individual level was possible. Also, results from a control group of epilepsy patients without antiseizure treatment were unavailable, complicating correction for unknown confounders. Additionally, no distinction was made for different ASMs or dosage, as the objective of the current study was to explore the relationship between overall ASM load and IQ and the sample size was too small to allow for analyses of ASM subgroups. Most children in our cohort used multiple ASM, often with different mechanisms of actions and with different cognitive side effect profiles, which complicates differentiating between the effects on intelligence of individual drugs.

Furthermore, a methodological limitation is the relatively small overall sample size, with unequal sizes of etiology subgroups. Finally, studies investigating the influence of epileptic seizures on IQ, while correcting for ASM use is scarce. Therefore, separating the effects of long-term medication use from those of ongoing seizures remains difficult.

Altogether, the observed relation must be confirmed in a prospective study with a representative sample from the whole epilepsy population while assessing the effect of ASM in different stages of neurodevelopment and exploring these effects for different subgroups of medications.

Conclusion

This study revealed a significant negative relation between ASM load and TIQ after adjustment for epilepsy-related confounders and the number of ASMs taken at the time of NPA. Changes in brain structure did not mediate this relation. Since the implications of the current study are considerable, the results have to be interpreted with caution and confirming a possible causal relation between medication load and IQ in a prospective, longitudinal study design is desirable. As a concluding remark, it must be mentioned that a potential effect of ASM may very well be justified compared to the detrimental effects of epilepsy itself and continuing seizures.

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Authors' contributions: For Author contributions, also see Appendix 1.

Ms. Stevering collected data, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Lamberink conceptualized and designed the study, collected data, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Woodfield processed the MR images and reviewed and revised the manuscript.

Prof. dr. Chin assisted in the analysis and interpretation of MR images and reviewed and revised the manuscript.

Dr. Bastin assisted in the analysis and interpretation of MR images and reviewed and revised the manuscript.

Dr. Van Schooneveld collected data and reviewed and revised the manuscript.

Prof. dr. Braun, Dr. Geleijns, and Dr. Otte conceptualized and designed the study and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Tables and figures

Box 1 Definitions

Aetiology of epilepsy: genetic, structural, metabolic, immune, infectious, unknown; according to International League Against Epilepsy classification[22].

Duration of active epilepsy: calculated as the difference between the date of first seizure and the date of last seizure expressed in years. Date of NPA or MRI was used when completed prior to the last seizure, or when the date of last seizure was unavailable.

Maximum seizure frequency: defined as the highest seizure frequency as noted in the patient's history before NPA was performed, expressed in seizures per day.

History of secondary generalised seizures: scored positively if a secondary generalised seizure was reported.

History of status epilepticus: scored positively if any case of status epilepticus requiring hospitalisation was reported. Status epilepticus was classified according to the International League Against Epilepsy guidelines[23].

Figure 1 Anatomical regions parcellated from T1-weighted MRI using Freesurfer. A representative left hemisphere is shown.

Legend: a) inferior axial slice, b) superior axial slice, c) posterior coronal slice, d) anterior coronal slice, e) medial sagittal slice, f) lateral sagittal slice. Regions shown: white matter (white), cerebral cortex (light blue), putamen (pink), pallidum (dark blue), thalamus (dark green), caudate (light brown), superior frontal gyrus (light green), caudal middle frontal gyrus (dark brown), precentral gyrus (purple), paracentral gyrus (red), cerebellum (yellow).

Table 1 Demographics

Variable	Mean (SD)/median (IQR; Q1 – Q3)/n (%)
Gender, female	31/59 (52.5%)
Age at first seizure, years	4.0 (1.2 – 5.5)
Age at first antiseizure treatment, years	4.6 (2.0 – 6.6)
Duration of active epilepsy*, at time of:	
MRI	4.1 (1.7 – 6.7)
NPA	4.1 (1.9 – 6.7)
Time between MRI and NPA§	-0.2 (1.9)
Etiology of epilepsy	
Structural	42 (71.2%)
Genetic	2 (3.4%)
Metabolic	1 (1.7%)
Infectious	1 (1.7%)
Immune	0 (0.0%)
Unknown	13 (22.0%)
Seizure frequency	
Maximum seizure frequency MRI per month†	91.3 (2.0 – 243.3)
Maximum seizure frequency NPA per month†	91.3 (2.0 – 243.3)
Seizure frequency near MRI per month‡	8.7 (0.2-121.7)
Seizure frequency near NPA per month‡	5.4 (0.2-76.0)
History of secondary generalized seizures	28 (47.5%)
History of status epilepticus	13 (22.0%)
Epilepsy focus based on EEG	
Right-sided	22 (37.3%)
Left-sided	31 (52.5%)
Unknown	6 (10.2%)
Pharmacoresistance	16 (27.1%)
Epilepsy surgery after MRI and NPA	30 (50.8%)
Age at MRI, years	8.79 (2.45)
Multiple MRIs performed	24 (40.7%)
MRI side of lesions	
Right-sided	15 (25.4%)
Left-sided	27 (45.8%)
No lesions	17 (28.8%)
Age at NPA, years	8.98 (2.31)
Multiple NPAs performed	24 (40.7%)
Number of antiseizure medications at NPA	1.7 (1.0)
Medication load in medication-years, at time of:	
MRI	4.9 (1.8 – 10.6)
NPA	5.3 (2.0 – 11.1)
During monotherapy	1.6 (0.6 – 3.3)
During polytherapy	1.7 (0.0 – 9.0)
Cortical thickness values in millimeters	
Mean cortical thickness	2.8 (0.2)
Precentral gyrus	2.6 (0.2)
Caudal middle frontal gyrus	2.8 (0.3)
Paracentral gyrus	2.7 (0.3)
Superior frontal gyrus	3.1 (0.3)
Volume values in cm3 (milliliter)	
Total hemisphere volume	537.5 (63.8)
White matter volume	180.9 (29.3)
White matter volume/total hemisphere volume (%)	33.6 (2.9)
Cerebellar volume	66.9 (8.6)
Cerebellar volume/total hemisphere volume (%)	12.5 (1.2)
Thalamus	7.0 (0.7)
Putamen	5.5 (0.9)
Pallidum	1.7 (0.3)
Intelligence quotient	
Total IQ (n=57)	77.4 (18.9)
Verbal IQ (n=54)	83.9 (18.2)
Performance IQ (n=52)	80.3 (15.0)

Continuous variables are depicted as mean ± SD, count variables as n (%), and non-normally distributed variables as median (IQR: 25th percentile – 75th percentile). SD = standard

deviation. n = number of patients. IQR = interquartile range. NPA = neuropsychological assessment. EEG = electroencephalography.
* = duration of active epilepsy, defined as date of first seizure till date of last seizure, up to the date of NPA/MRI, expressed in years.
† = maximum seizure frequency that was reported at any time before NPA/MRI was performed, expressed as number of seizures per month.
‡= the current seizure frequency reported near the time of NPA/MRI, expressed as number of seizures per month.
§ = time between NPA and MRI in years; calculated at 'age at MRI' – 'age at NPA'.

Table 2 The relation between ASM load and IQ

	Total IQ RC (CI)	p value	Model R^2	**Verbal IQ** RC (CI)	p value	Model R^2	**Performance IQ** RC (CI)	p value	Model R^2
Crude model ASM load in medication-years	-1.68 (-2.24 to -1.12)	<0.001	0.40	-1.52 (-2.24 to -0.79)	<0.001	0.25	-1.17 (-1.85 to -0.49)	0.001	0.19
Adjusted model ASM load in medication-years	-1.16 (-2.01 to -0.30)	0.01	0.43	-0.86 (-1.92 to 0.21)	0.11	0.29	-1.04 (-2.07 to -0.001)	0.05	0.20

The adjusted model was corrected for potential confounders by using a propensity score computed of the variables 'duration of active epilepsy', 'age at first antiseizure medication treatment', 'etiology of epilepsy', 'history of secondary generalized seizures, 'history of status epilepticus', 'maximum seizure frequency per month', 'number of antiseizure medications at time of neuropsychological assessment (NPA)'. ASM load = antiseizure medication load (at time of NPA). IQ = intelligence quotient. RC = regression coefficient. CI = 95% Confidence Interval. p value = p value indicating the significance of the regression coefficient. R^2 = determination coefficient, which concerns the model in total.

Figure 2 The association between antiseizure medication load and intelligence quotient

Legend: This figure represents the association between the antiseizure medication (ASM) load and intelligence quotient (IQ). Simple regression lines for total IQ, verbal IQ and performance IQ are shown.
ASM load = antiseizure medication load. IQ = intelligence quotient.

Table 3 The relation between antiseizure medication load and brain structure in the unaffected hemisphere

Used outcome measure	**Crude model** ASM load* (n=59) RC (CI)	p value	Model R^2	**Adjusted model** ASM load* (n=59) RC (CI)	p value	Model R^2
Cortical thickness (in millimeter)						
Mean cortical thickness	0.004 (0.00 to 0.01)	0.21	0.03	0.01 (0.002 to 0.02)	0.02	0.09
Caudal middle frontal gyrus	0.004 (-0.01 to 0.02)	0.59	0.01	0.02 (-0.003 to 0.04)	0.10	0.06
Paracentral gyrus	0.003 (-0.01 to 0.02)	0.66	0.00	0.01 (-0.01 to 0.03)	0.51	0.01
Precentral gyrus	-0.001 (-0.01 to 0.01)	0.82	0.00	0.01 (-0.01 to 0.24)	0.20	0.06
Superior frontal gyrus	0.006 (-0.01 to 0.02)	0.37	0.01	0.01 (-0.01 to 0.03)	0.16	0.03
Volume in cm3 (milliliter)						
Total hemisphere volume	-0.24 (-2.93 to 2.45)	0.86	0.00	2.13 (-1.98 to 6.23)	0.30	0.04
White matter/THV (%)	-0.48 (-3.58 to 2.62)	0.76	0.00	0.08 (-4.75 to 4.91)	0.97	0.00
Cerebellar volume/THV (%)	-1.34 (-4.04 to 1.36)	0.33	0.02	-2.42 (-6.61 to 1.77)	0.25	0.03
Pallidum	0.01 (0.00 to 0.02)	0.19	0.03	0.01 (-0.01 to 0.02)	0.35	0.30
Putamen	-0.01 (-0.05 to 0.02)	0.46	0.01	-0.03 (-0.08 to 0.03)	0.37	0.02
Thalamus	0.003 (-0.03 to 0.03)	0.84	0.00	0.01 (-0.03 to 0.06)	0.56	0.01

The adjusted model was corrected for potential confounders by using a propensity score computed using the variables 'duration of active epilepsy', 'age at first antiseizure treatment', 'history of status epilepticus', 'history of secondary generalized seizures', 'etiology of epilepsy', 'maximum seizure frequency per month'. The maximum seizure frequency per month at any time before MRI was included. Duration of active epilepsy, defined as date of first seizure till date of last seizure, or till date of MRI when epilepsy was still active at the time of MRI, was expressed in years.

ASM load = antiseizure medication load (at time of MRI). RC = regression coefficient. CI = 95% Confidence Interval. p value = p value which indicates the significance of the regression coefficient, $p < 0.0045$ was considered statistically significant (Bonferroni correction for multiple testing). THV = total hemisphere volume. * = antiseizure medication load at time of MRI was included.

Table 4 The relation between brain structure in the unaffected hemisphere and IQ presented as regression coefficients (RC)

Structural measure used as independent variable	Crude model RC (CI)	p value	Model R^2	Adjusted model RC (CI)	p value	Model R^2
Total IQ (n=57)						
Cortical thickness in mm						
Mean cortical thickness	-7.13 (-37.83 to 23.58)	0.64	0.00	-18.11 (-54.02 to 17.80)	0.32	0.03
Caudal middle frontal gyrus	-2.22 (-17.52 to 13.09)	0.77	0.00	-5.78 (-23.83 to 12.27)	0.52	0.01
Paracentral gyrus	-4.37 (-21.56 to 12.82)	0.61	0.01	-9.89 (-29.83 to 10.06)	0.33	0.03
Precentral gyrus	-2.86 (-24.99 to 19.27)	0.80	0.00	-18.10 (-42.72 to 6.53)	0.15	0.10
Superior frontal gyrus	-3.93 (-20.27 to 12.42)	0.63	0.00	-4.50 (-22.72 to 13.71)	0.62	0.01
Volume in cm3 (milliliter)						
Total hemisphere volume	0.07 (0.00 to 0.15)	0.06	0.06	0.05 (-0.04 to 0.13)	0.28	0.08
White matter/THV (%)	-0.02 (-0.10 to 0.06)	0.62	0.01	-0.02 (-0.10 to 0.06)	0.55	0.01
Cerebellar volume/THV (%)	0.03 (-0.06 to 0.11)	0.53	0.01	0.02 (-0.06 to 0.11)	0.58	0.01
Pallidum	2.59 (-17.61 to 22.79)	0.80	0.00	10.20 (-14.46 to 34.85)	0.41	0.02
Putamen	5.82 (0.39 to 11.25)	0.04	0.08	5.24 (-0.97 to 11.46)	0.10	0.08
Thalamus	7.93 (3.55 to 15.51)	0.04	0.07	7.15 (-0.98 to 15.27)	0.08	0.08
Verbal IQ (n=54)						
Cortical thickness in mm						
Mean cortical thickness	-2.47 (-33.27 to 28.34)	0.87	0.00	-16.39 (-52.83 to 20.04)	0.37	0.04
Caudal middle frontal gyrus	-2.01 (-18.17 to 14.16)	0.80	0.00	-5.58 (-25.42 to 14.26)	0.58	0.01
Paracentral gyrus	-7.02 (-24.64 to 10.59)	0.43	0.01	-14.75 (-35.45 to 5.96)	0.16	0.05
Precentral gyrus	-2.69 (-25.30 to 19.91)	0.81	0.00	-18.99 (-44.90 to 6.93)	0.15	0.10
Superior frontal gyrus	-6.87 (-24.09 to 10.36)	0.43	0.01	-10.73 (-30.64 to 9.18)	0.28	0.02
Volume in cm3 (milliliter)						
Total hemisphere volume	0.07 (-0.01 to 0.15)	0.08	0.06	0.04 (-0.04 to 0.12)	0.35	0.12
White matter/THV (%)	-0.001 (-0.07 to 0.07)	0.98	0.00	0.00 (-0.07 to 0.07)	0.99	0.00
Cerebellar volume/THV (%)	0.001 (-0.08 to 0.08)	0.98	0.00	-0.02 (-0.09 to 0.06)	0.71	0.04
Pallidum	-0.48 (20.57 to 19.61)	0.96	0.00	-1.04 (-25.53 to 23.45)	0.93	0.00
Putamen	4.15 (-1.37 to 9.67)	0.14	0.04	1.89 (-4.34 to 8.11)	0.55	0.08
Thalamus	5.31 (-2.05 to 12.67)	0.15	0.04	3.79 (-4.02 to 11.59)	0.33	0.06
Performance IQ (n=52)						
Cortical thickness in mm						
Mean cortical thickness	7.11 (-18.13 to 32.34)	0.57	0.01	0.01 (-30.29 to 30.32)	1.00	0.02
Caudal middle frontal gyrus	6.31 (-6.25 to 18.88)	0.32	0.02	5.04 (-10.23 to 20.31)	0.51	0.02
Paracentral gyrus	0.81 (-13.25 to 14.86)	0.91	0.00	-4.06 (-20.93 to 12.81)	0.63	0.02
Precentral gyrus	1.35 (-16.79 to 19.48)	0.88	0.00	-9.15 (-30.23 to 11.92)	0.39	0.07
Superior frontal gyrus	5.13 (-8.45 to 18.71)	0.45	0.01	4.76 (-10.53 to 20.04)	0.54	0.01
Volume in cm3 (milliliters)						
Total hemisphere volume	0.04 (-0.03 to 0.10)	0.25	0.03	0.03 (-0.04 to 0.10)	0.42	0.03
White matter/THV (%)	-0.01 (-0.06 to 0.05)	0.87	0.00	-0.002 (-0.06 to 0.06)	0.95	0.00
Cerebellar volume/THV (%)	0.002 (-0.06 to 0.07)	0.94	0.00	-0.004 (-0.07 to 0.06)	0.90	0.01
Pallidum	7.97 (-9.94 to 25.88)	0.38	0.02	15.16 (-6.19 to 36.51)	0.16	0.05
Putamen	2.58 (-2.02 to 7.18)	0.27	0.03	2.86 (-2.44 to 8.15)	0.28	0.03
Thalamus	7.02 (1.31 to 12.73)	0.02	0.11	7.58 (1.41 to 13.74)	0.02	0.11

The adjusted model was corrected for potential confounders by using a propensity score computed using the variables 'duration of active epilepsy', 'age at first antiseizure medication treatment', 'etiology of epilepsy', 'history of secondary generalized seizures, 'history of status epilepticus', 'maximum seizure frequency per month', 'number of antiseizure medications at time of neuropsychological assessment (NPA)'. The maximum seizure frequency per month at any time before NPA was included. Duration of active epilepsy, defined as date of first seizure till date of last seizure, or till date of NPA when epilepsy was still active at the time of NPA, was expressed in years.

RC = regression coefficient. CI = 95% Confidence Interval. p value = p value which indicates the significance of the regression coefficient, $p < 0.0045$ was considered statistically significant (Bonferroni correction for multiple testing). n = number of patients included in the analysis. THV = total hemisphere volume.

Appendix 1: Authors

Name, location, role, contribution

Name	Location	Role	Contribution
Carmen H. Stevering MD	University Medical Hospital Utrecht, the Netherlands	Author	Collected data, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript.
Herm J. Lamberink MD PhD	University Medical Hospital Utrecht, the Netherlands	Author	Conceptualized and designed the study, collected data, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript.
Julie Woodfield MBChB	University of Edinburgh, Scotland	Author	Processed the MR images, and reviewed and revised the manuscript.
Monique van Schooneveld PhD	University Medical Hospital Utrecht, the Netherlands	Author	Collected data, and reviewed and revised the manuscript.
Willem M. Otte PhD	University Medical Hospital Utrecht, the Netherlands	Author	Conceptualized and designed the study, and reviewed and revised the manuscript.
Richard F.M. Chin PhD	University of Edinburgh, Scotland	Author	Assisted in analysing and interpreting the MR images, and reviewed and revised the manuscript.
Mark E. Bastin PhD	University of Edinburgh, Scotland	Author	Assisted in analysing and interpreting the MR images, and reviewed and revised the manuscript.
Karin Geleijns MD PhD	University Medical Hospital Utrecht, the Netherlands	Author	Conceptualized and designed the study, and reviewed and revised the manuscript.
Kees P.J. Braun MD PhD	University Medical Hospital Utrecht, the Netherlands	Author	Conceptualized and designed the study, and reviewed and revised the manuscript.

Test yourself - multiple choice questions

Question 1: How was cumulative antiseizure medication load calculated in this study?
a) Cumulative medication load was calculated by adding the number of antiseizure drugs that were taken during the follow-up period.
b) Cumulative medication load was calculated by adding the years each antiseizure drug was taken, corrected for dosage, until the neuropsychological assessment.
c) Cumulative medication load was calculated by adding the years each antiseizure drug was taken until the neuropsychological assessment.

Question 2: This study evaluated whether the relation between antiseizure medication and IQ was mediated by changes in cortical thickness and brain volume. What were the specific brain areas studied?
a) Cortical thickness was evaluated in the superior frontal gyrus, precentral gyrus, caudal middle frontal gyrus and paracentral gyrus.
b) Cortical thickness was evaluated in thalamus, pallidum, putamen and superior frontal gyrus.
c) Cerebral volume was evaluated for total brain volume, white matter volume, cerebellar volume, thalamus, putamen, pallidum and hippocampus.

Question 3: How should the relation between antiseizure medication load and total IQ be interpreted?
a) An increase of antiseizure medication load of one medication-year resulted in a decrease in total IQ of 1.2 points.
b) When the number of antiseizure medications increased with one, total IQ decreased with 1.2 points.
c) When a child was on two antiseizure medications during a period of one year, our study results revealed a decrease in total IQ of 1.2 points.