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Evaluating the mediating role of executive functions for antiepileptic drugs' effects on IQ in children and adolescents with epilepsy

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ABSTRACT

Several studies suggest that antiepileptic drug (AED) treatment may permanently or reversibly affect intelligence (intelligence quotient [IQ]) in children and adolescents with epilepsy. Since AED treatment preferentially affects attention and executive functions, we evaluated the potentially mediating effect of executive functions in regard to the adverse effects of drug treatment on intelligence.

In a retrospective observational study, 178 children and adolescents with refractory and mostly localization-related epilepsies were evaluated in regard to the interrelation of IQ (Wechsler Intelligence Scale for Children [WISC III] short-form), executive functions (EpiTrack-Junior®, a cognitive AED screening test), and drug treatment (drug load).

The results indicate that a low IQ was evident in 23%, impaired executive functions in 59% of the patients. Executive functions correlated to IQ ($r = 0.60$) and the symbol digits and picture arrangement subtests ($R^2 = 0.46$) in particular. Odds ratios for impaired executive functions compared to being off drug (33% impaired) increased from 2.0 with one drug (53% impaired) to 9.5 (83% impaired) with at least three drugs. A mediation analysis revealed that drug dependent differences in executive functions mediate the negative effect of the AED load on intelligence.

Hence, executive functions appear to link adverse cognitive side effects of AED treatment to intelligence. Considering Catell's two factor model of intelligence, AEDs preferentially affect the aspects of fluid intelligence. The overall impact of AED on intelligence appears mild. It may become relevant, however, when drug-induced impairments persist over longer time intervals during sensitive developmental phases. This issue needs to be addressed in future longitudinal studies.

1. Introduction

Antiepileptic drug (AED) treatment is efficacious in controlling seizures in many patients with epilepsy (PWE) but bears the risk of side effects on cognitive functioning. These can be positive given that the drug has cognition enhancing effects or given that drugs control seizures and epileptic activity, but often they are negative [1,2]. There is now an increased awareness in regard to this issue in epileptology, and physicians have options to overcome cognitive adverse events in their routine praxis [3]. As regards children, it is now widely accepted that intrauterine exposure to AEDs may negatively affect neurocognitive development of children born to mothers with epilepsy. Such teratogenic effects were already reported in the 1990s for phenytoin, phenobarbital, and primidone [4–7]. More recent studies reported adverse effects of fetal exposure to sodium valproate (VPA) on the children's neuronal and cognitive development [8–10]. In one of these studies, intelligence in three-year-old children with intrauterine exposure to VPA was almost two-thirds of one standard deviation (SD) lower (i.e., about 9 intelligence quotient [IQ] points) than in children exposed to comparator drugs [10]. These children still suffered from a significantly poorer cognitive development at 6 years of age [11]. Also, animal experiments in rat models confirmed adverse effects of intrauterine VPA exposure on cognitive and behavioral brain functions and even structures [12,13]. This and confirmatory evidence from additional studies meanwhile resulted in guidelines for AED treatment of female PWE of childbearing age [14]. However, the question of whether and to which extent antiepileptic pharmacotherapy in children with epilepsy (CWE) interferes with their brain and intellectual development is still unanswered. It would be of high clinical relevance to know how the risk of cognitive adverse AED effects could be handled in therapeutic decision making in individual patient care.

Previous studies, despite heterogeneous settings with diverse designs and different psychometric measures unambiguously, show a risk for cognitive and behavioral adverse effects of AEDs in children and adolescents [1,2]. Depending on the specific substance, drug regimen (mono- versus polytherapy), titration speed, and drug dosage, AEDs negatively affect attention, memory, mental speed, verbal fluency,

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word finding, working memory, and language (both expressive and receptive) [1,2,15]. In addition, some reports claim that intelligence (or the IQ) can be impaired by AED treatment [16]. Being one of the most ecologically valid psychometric measures [17], IQ reflects a child's global intellectual functioning in comparison to its peers. The global IQ is predictive for academic achievement and thus highly indicative of a child's overall cognitive and psychosocial developments. Negative impact on intelligence in CWE has been reported for phenobarbital [18,19] and, more recently, topiramate [20,21] and valproic acid [16]. Follow-up studies on the cognitive development of children who successfully underwent epilepsy surgery demonstrated significant IQ improvement because of AED withdrawal, however without referring to a specific drug [22,23]. Different from adult patients, a major issue in pediatric patients is that even if the cognitive side effects of AEDs are principally reversible, the children might miss important neurodevelopmental steps when they are treated with cognitively disabling drugs for a longer period of time [24].

The present study investigated the relationship between AED treatment and intelligence in CWE. We followed the hypothesis that effects of AED on IQ might be mediated by executive functions. Following Catell's structural model of intelligence, full-scale IQ comprises at least two ability factors, crystallized intelligence, i.e., habits, skills, and knowledge which to a high degree reflect the level of education, and fluid intelligence, i.e., the level of performance in basic cognitive operations which are supposed to be less influenced by education and the cultural or ethnic background [25]. Fluid intelligence is strongly connected to executive functions which in turn represent a good predictor of overall intelligence [26]. Executive functions comprise higher order cognitive functions including working memory, task switching, and phonemic fluency etc. Besides potential drug-specific effects on psychomotor speed, language, or declarative memory, almost all AEDs with known cognitive side effects show a possible negative impact on executive functions as well [3,27]. Accordingly, executive functions are well-suited for the monitoring of AED-induced cognitive side effects [28].

2. Materials and methods

2.1. Subjects

This retrospective observational cross-sectional study evaluated 178 children and adolescents aged 6–17 years mostly with localization-related (i.e., symptomatic or cryptogenic) epilepsies who had been admitted to a tertiary epilepsy center (University of Bonn Medical Center, Department of Epileptology, Bonn, Germany) for advanced diagnostic evaluation. Neuropsychological assessment was an integral part of this evaluation. Included were children who had been evaluated in regard to intelligence and executive functions. Excluded were CWE who did not allow formal testing.

Table 1 shows the patient characteristics. Overall, 178 children and adolescents fulfilled the inclusion criteria. The average age was 13.9 (SD: 2.6) years, and sex was distributed equally. The mean age at epilepsy onset was 8.3 (SD: 4.8) years; the mean duration of epilepsy was 6.2 (SD: 4.5) years. The mean monthly seizure frequency was 20.5 (SD: 42.0) per month, irrespective of the type of seizure. Since the dataset was anonymized, the patients' files were not accessible. According to the extracted notes on imaging, in 55% of the patients, a lesion was reported (mostly frontal and temporal); in a very small subgroup, explicitly, no lesion was reported but a focus of the epileptic activity indicative for focal epilepsy (7%); and in another small subgroup (5%), no magnetic resonance imaging (MRI) lesion and no focus were reported.

In 33%, no MRI- and electroencephalographic (EEG)-data were not reported. Since we do not know whether in these patients imaging had been performed and whether it was positive or negative and since apart from the diagnosis of epilepsy EEG has not been described as compatible with focal or generalized epilepsy, we define this group as unclear. We thus cannot exclude genetic epilepsies. Two of the unclear patients had the differential diagnosis of autoimmune encephalitis, two children had idiopathic generalized epilepsy (IGE), and one child the diagnosis of Rolando epilepsy.

Table 1
Demographic and clinical characteristics.

Sample size	N	178
Sex (male/female)	%	52/48
Age (years) (range: 6–17 yrs.)	M (SD)	13.9 (2.6)
Age at epilepsy onset (years)	M (SD)	8.3 (4.8)
Duration of epilepsy (years)	M (SD)	6.2 (4.5)
Pathology (MRI):		
• Lesional	N (%)	96 (55)
• Nonlesional		
-With epileptic focus	N (%)	13 (7)
-Without epileptic focus	N (%)	9 (5)
• Unclear	N (%)	57 (33)
Monthly seizure frequency	M (SD)	20.5 (42.0)
AED load:	M (SD)	1.6 (0.8)
• Off drug	N (%)	18 (10)
• Monotherapy	N (%)	65 (37)
• 2 drugs	N (%)	73 (41)
• 3 drugs	N (%)	18 (10)
• 4 drugs	N (%)	4 (2)
Intelligence (IQ)	M (SD)	93.2 (13.7)

AED, antiepileptic drug.

2.2. Diagnostic tools

Intelligence was assessed by a short-form of the German version of the Wechsler Intelligence Scale for Children (WISC-III). The short-form was used to limit the diagnostic burden for the children and to save resources for the administration of cognitive measures which evidentially are known to be more sensitive to clinical aspects of epilepsy than the full-scale IQ. The short-form extrapolates the total IQ from a smaller subset of the most indicative subtests by using a linear regression formula. For the German version of the WISC, the short-form comprises five out of ten subtests, i.e., block design, picture arrangement, symbol-digits, information, and vocabulary, and the IQ is calculated on the basis of a regression formula [29]. As a convention, the distribution of the IQ is defined by a mean of 100 and a SD of 15. Accordingly, any IQ < 85 (i.e., mean–1SD) has been considered as indicative for impaired intelligence.

Executive functions were assessed by the EpiTrack-Junior (ETJ), a short and easily applied screening tool for executive functions which was standardized for use in school-aged children and adolescents aged 6–18 years. The tool has been proven to be sensitive for cognitive AED side effects [30,31]. EpiTrack-Junior comprises six subtests addressing psychomotor speed (trail making test), mental flexibility (trail making test requiring switching between categories), response inhibition (inverse reading of the numbers 1 = "two" and 2 = "one"), verbal fluency (phonemic fluency), visuo-motor planning and anticipation (maze), and working memory (digits backward). The duration of test administration is usually below 20 min including scoring. Based on the normative data, the subtest raw scores are transformed into subtest value scores which are then summarized into a total score. The total score undergoes correction for age and finally results in the ETJ score. The ETJ score is normally distributed (mean: 33, SD: 2). According to the test norms, any ETJ score < 31 is considered as indicator of impaired executive functions.

2.3. Drug load

Antiepileptic drug load was defined as the number of concomitant AEDs that a patient was taking at the time of the assessment. A recent study had demonstrated that number of AEDs is an excellent marker for the total drug load that can be used in exchange to the cumulative defined daily dose (DDD) according to World Health Organization (WHO) standards which requires costlier calculations [32]. The same study demonstrated a stable negative relation between total AED load and performance in executive functions when statistically controlling for clinical indicators of epilepsy severity.

2.4. Statistical analyses

All statistics were calculated with IBM SPSS Statistics Version 25.

The percentages of patients with impaired intelligence or executive functions are reported descriptively on the basis of the cut-off scores stated above. In addition, odds ratios for the impairment of intelligence or executive functions were calculated for each number of AEDs with reference to patients being off drug.

Correlations of the cognitive performance scores (IQ and ETJ score) and the AED load were calculated using bivariate Pearson's product–moment correlation coefficients (r).

To answer the study's central question, we performed a mediation analysis based on linear regression analyses with a subsequent Sobel-Z-test. The prediction was that the relation of drug treatment and IQ is explained/driven by the effect of AED on executive functions.

p-Values below .05 (two-sided) were considered statistically significant.

3. Results

The mean IQ of the analyzed sample was 93.2 (SD: 13.7) with 23% of the patients showing intellectual impairment (IQ < 85). The mean ETJ score on executive functions was 28.2 (SD: 5.3) with 59% of the patients showing an impairment (ETJ score < 31).

The average AED load was 1.6 (SD: 0.8) with 10% of the patients being off drug, 37% on monotherapy, and 53% on polytherapies with 2, 3, or 4 AEDs. The Supplementary Table lists all drugs that were taken. Levetiracetam, lamotrigine, oxcarbazepine, and VPA were prescribed most often, both in monotherapy and in combination with other AEDs.

Table 2 shows the bivariate correlations between AED load, IQ, executive functions, and seizure frequency. Executive functions and IQ were correlated with high statistical significance (r = 0.60, p < .000; see also Fig. 1). Both measures of cognitive performance in turn were significantly correlated with AED load (r = 0.30, p < .001 and r = 0.197, p < .01). Seizure frequency as a marker of disease severity showed a positive correlation with drug load (r = 0.17, p < .05), as a nonsignificant trend it correlated with IQ (−0.16, p = .05), and it was not at all related to the ETJ score (r = −0.08, n.s.; see Table 2).

Figs. 2 & 3 show the average performance regarding intelligence (IQ) (Fig. 2) and executive functions (Fig. 3) depending on the AED load. In the off-drug condition, none (0%) of CWE showed impaired intelligence, but 33% of these children showed impaired executive functions. These frequencies increased to 20% and 51% under monotherapy, to 29% and 65% under treatment with two AEDs, and to 26% and 83% under polytherapy with 3 or 4 drugs, respectively. Fig. 3, in addition, shows the increase of the odds ratios for cognitive impairments under AED mono- and polytherapy as compared to the frequency of impairments in the off-drug condition. With 3 or 4 drugs, the risk of impaired executive functions is 9.5 fold ($\chi^2 = 10.3$, p < .01). The risk of a low IQ under treatment varies between 1.3 and 1.5 ($\chi^2 = 7.1$, p < .01) under treatment when compared to the off-drug condition.

The results of the mediation analysis that represents the decisive statistics in regard to the main question of this study are depicted in Fig. 4. First of all, the total AED load is indeed a significant predictor of intelligence as demonstrated by **path c** (Fig. 4). To prove the potential mediating role of executive functions, it is essential that (1) performance in executive functions can be significantly predicted by the total AED load (**path a**), and that (2) performance in executive functions significantly predicts intelligence despite concomitant consideration of the AED load (**path b**). Both conditions are fulfilled (Fig. 4), and the Sobel-Z-test statistics (p = .0001) confirms that the negative effect of antiepileptic treatment on intelligence is driven by drug-mediated performance differences in executive functions. Moreover, since the direct

Table 2
Bivariate correlations (Pearson's r) of antiepileptic drug load, intelligence, and executive functions (N = 175).

	AED load	Executive functions (ETJ score)	Intelligence (IQ)
Seizure frequency	−0.17*	−0.08 n.s.	−0.16 n.s.
AED load (number of AEDs)		−0.30***	−0.20**
Executive functions (ETJ score)			+0.60***

n.s. not significant.
AED, antiepileptic drug; ETJ, EpiTrack-Junior.
*** p < .001.
** p < .01.
* p < .05.

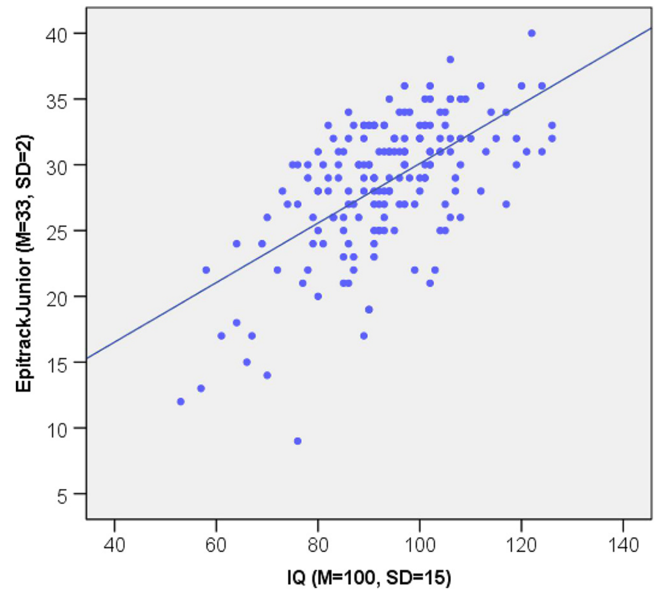

Fig. 1. Bivariate correlation between intelligence (IQ) and executive functions (ETJ score) in children with epilepsy (N = 178).

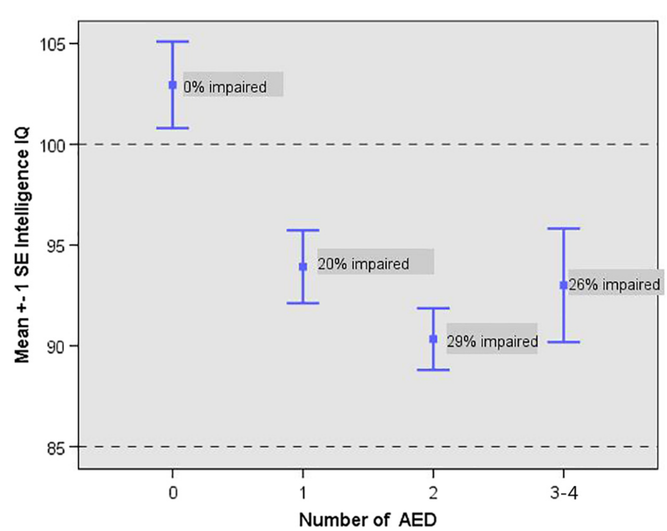

Fig. 2. Intelligence IQ (WISC/WAIS-R) as a function of the antiepileptic drug load (i.e., number of AED). The annotations report the percentage of impaired children and adolescents. Dotted lines indicate the age-adjusted mean and standard deviations, also representing the range of impairment (i.e., score < mean–1 SD).

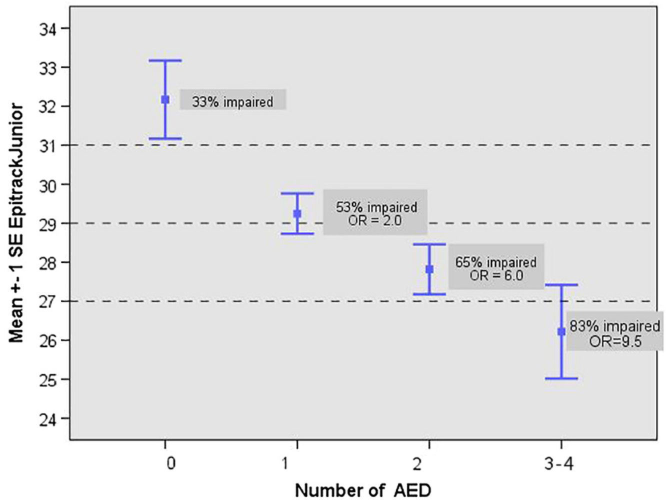

Fig. 3. Executive functions (EpiTrack-Junior) as a function of the antiepileptic drug load (i.e., number of AED). The annotations report the percentage of impaired children and adolescents and the odds ratios of being impaired under the respective AED treatment regimen when compared to the off-drug condition. Dotted lines indicate the age-adjusted mean and standard deviations, also representing the range of impairment (i.e., score < mean–1 SD).

effect (**path c'**) of AED load on intelligence is no longer significant when considering the mediator variable, the model indicates complete (vs. partial) mediation.

Table 3 shows the results of a stepwise regression analysis indicating that of the WISC subtests, the "symbol digit" and the "picture arrangement" tests predict about 46% of the executive performance (ETJ score) while the block design, the vocabulary, and the information subtests did not enter the equation.

4. Discussion

Children with epilepsy and especially those with difficult-to-treat epilepsies have an increased risk for neurocognitive impairment and developmental hindrance. Cognitive impairment is already present in untreated children with newly diagnosed epilepsy indicating the cognitive risks resulting from seizures and the underlying pathological brain condition [33]. If possible, AED treatment should not add to this. In the framework of intrauterine exposure to AEDs, the possibility of sustained adverse cognitive effects on brain development is now widely acknowledged but what about the situation of CWE who are in need of (direct) AED treatment?

Associations between drug treatment and IQ have been repeatedly described in children and adolescents, and the present study evaluated the question of whether AED might affect IQ particularly via their known impact on executive functions.

First, we found a strong positive correlation between executive functions and intelligence confirming the close relationship of both cognitive domains as it has been hypothesized and as it has been demonstrated before [26]. The WISC is not constructed according to Cattell's two factor model of crystallized and fluid, but the data confirm that the EpiTrack is mainly correlated with those IQ subtests (symbol digit and the picture arrangement) which require high degrees of attention and mental flexibilities. This is in line with recent findings in children with absence epilepsies. In this group, ETJ performance was differentially correlated with the "working memory index" of the Wechsler Intelligence Scale (version IV) but not with the "psychomotor speed" or the "verbal comprehension" indices of that test battery. EpiTrack-Junior, in addition, was neither correlated with measures of verbal or nonverbal memory [34].

Of note, the correlation between executive functions and intelligence did not result from a methodological artifact as both test

Table 3
Stepwise regression analysis: Epitrack and IQ subtests.

a)		
Regression	Predictors/beta coefficients	t-Value/ significance
EpiTrack Junior	Symbol digits	6.14/p < .001
r-Square = 0.46	0.46	
F = 49.2, p < .001	Picture arrangement	4.67/p < .001
	0.35	

Excluded: block design, vocabulary, information.

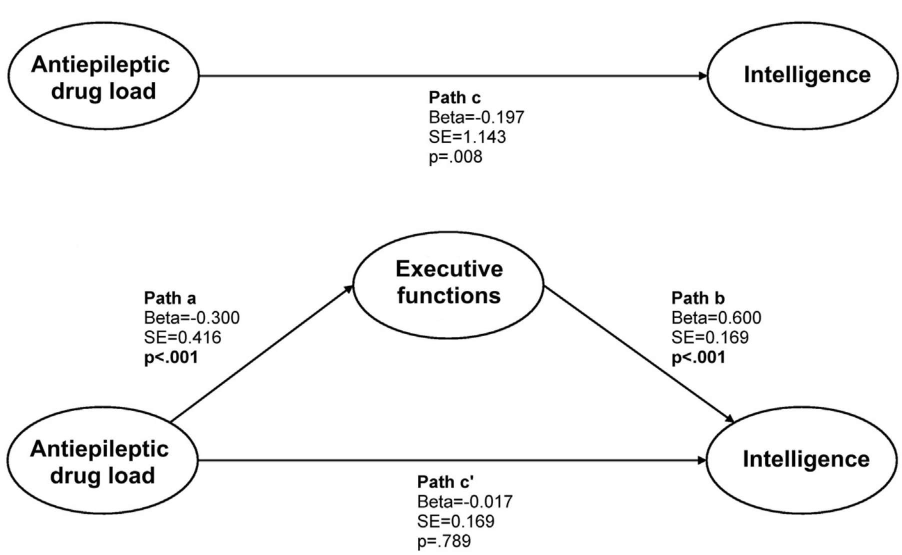

Fig. 4. Mediation analysis indicating that the significant total effect of antiepileptic drug load on intelligence (path c) is lost, when performance in executive functions is introduced as mediator variable (path c'). The significant indirect negative effect of antiepileptic drug load on intelligence via executive functions (path a ➔ path b) is confirmed by Sobel-Z-test statistics (p = .0001). Taken together, the model characteristics point to a complete (vs. partial) mediation effect of executive functions regarding the relationship between antiepileptic drug load and intelligence.

batteries used different tasks (e.g., digit backwards is not part of WISC, version III).

Second, the present study indicates a negative relationship between AED load, i.e., the number of concomitant AEDs, and both the children's intelligence and even more so executive functioning. Impairments in executive functions and IQ increased from 33% and 0% without treatment to 83% and 26% impaired CWE taking 3 or 4 AEDs in polytherapy. That impairments are frequent without the influence of AED and also before AED treatment is initiated has been shown before. Our finding of 33% impaired CWE being off drug is close to the 28% impaired children found in children with mixed etiologies before treatment was initiated [31]. This number also parallels the finding of 31% impaired CWE being off drug reported in the standardization and validation study of the EpiTrack in children in 2010 [30]. In the latter study 86% CWE were impaired with three and more drugs. Here it were 83%.

Correlation does not necessarily imply causality. However, two recent longitudinal studies confirmed significant gains in IQ in CWE when drugs were tapered or withdrawn after successful epilepsy surgery, and these IQ gains were independent of the seizure outcome [22,23]. Comparably, significant and selective improvement of executive functions because of drug load reduction after successful epilepsy surgery was found in adult PWE [35].

Third, the correlation of drug load and IQ was significant but small compared with the correlation to executive functions. Based on the assumption that AED mainly affects psychomotor speed, attention, and executive functions, IQ which is an aggregate measure of knowledge and different mental operations understandingly must be less affected.

Fourth, the results of the mediation analysis indicate that the negative effect of AED load on intelligence correlation is almost completely mediated by drug-induced performance differences in executive functions [32]. Surely, controlled longitudinal studies are required to demonstrate that an increase or decrease of the AED load is leading to IQ changes as a function of the drug dependent effects on executive functions, respectively. Unfortunately, the two studies in postsurgical children mentioned above did not evaluate the data on a subtest level which could have evidenced a stronger role for the fluid aspects of intelligence nor did they include explicit measures of executive functioning [22,23]. Future studies should make this differentiation and should as well address the question of whether the time interval during which executive functions/fluid intelligence are negatively affected by drug treatment has effects on the acquisition of knowledge/crystallized intelligence.

One disadvantage of the present study is its cross-sectional design. As mentioned above, longitudinal studies are required to proof the relation between drug treatment executive functions and IQ suggested here on the basis of cross-sectional results. It may well be that lasting drug-induced impairment during sensitive phases of development result in developmental delay or even hindrance. This needs to be addressed with studies with follow-up evaluation spanning periods of time which are long enough to reveal the impact of treatment on cognitive development. Prospective studies with a control condition or even randomization, however, are difficult to set up since one would not want to randomize children to less vs. more potentially harmful drugs or to mono- vs. polypharmacotherapy irrespective of the seizure situation. Studying recovery and intellectual catch up in a withdrawal study design in seizure-free (from poly- vs. monotherapy to off drug [22,23]) or even not seizure-free children (from multiple drugs to one or two drugs [36]) at different developmental steps appears to be a good alternative. One would predict that first the executive functions and functions of fluid intelligence recover and that later there will be an effect of this release on knowledge acquisition and functions of crystallized intelligence.

Another critical point is that the evaluated group was quite heterogeneous and pharmacoresistant which may represent a kind of bias. However, the primary aim of this study was to evaluate AED effects on cognition independent of the epilepsy. Comparing AED effects on cognition in different homogeneous patient cohorts would surely be an issue of future interest.

Finally, a higher AED load may simply reflect more severe epilepsy. In fact, AED load was correlated with seizure frequency which tended to correlate also with IQ (i.e., more seizures in those with lower IQ). Executive functions, however, appeared independent of seizure frequency. That the correlation between executive functions and AED load is only marginally determined by different markers of disease severity has recently been demonstrated in a large study in adult PWE [32].

Taking these limitations into account, we can conclude that we were able to confirm again the close relation of AED treatment (drug load) and executive functions of CWE as assessed by the ETJ. In addition, a correlation between drug treatment and IQ could be discerned. We further confirmed the hypothesis that executive functions are highly related to IQ, and that the observed effects of drug treatment on IQ are mediated by executive functions. This finding may explain past reports which found change in full-scale IQ measures related to changes in drug treatment. Overall, we want to raise concerns that principally reversible adverse effects of AED on cognition may cause intellectual problems in CWE when this lasts for a longer period of time. Thus, monitoring cognition along with drug treatment seems advisable.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.04.003.

Contributors

C. Helmstaedter provided the statistical data analysis and wrote the first draft of the manuscript. J.-A. Witt contributed to the statistical data analysis by performing the mediation analysis, and he significantly revised the manuscript. C. Hoppe collected and organized the data for later analysis and provided the final version of the manuscript.

Declaration of interests

C. Helmstaedter reports grants by the EU (E-Pilepsy, EpiCare), personal honoraries, and travel support for counseling and talks UCB, GW pharma, EISAI, and license fees by UCB and EISAI outside this work. J.-A. Witt has received honoraria from UCB and Eisai, outside the submitted work. C. Hoppe reports no competing interests as regards the submitted work.

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Ethical approval

Ethical approval for local (and centralized multicenter) data collection as part of a registry was given by the Ethic Committee of the University Clinic Bonn. #002/17. The dataset was extracted from this database and was anonymized for retrospective evaluation.

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