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Manuscript title: Interictal epileptiform discharges have an independent association with cognitive impairment in children with lesional epilepsy

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Summary

Objectives: The relative contribution of interictal epileptiform discharges (IED) to cognitive dysfunction in comparison with the underlying brain pathology is not yet understood in children with lesional focal epilepsy.

Methods: The current study investigated the association of IED with intellectual functioning in 103 children with medication-resistant focal epilepsy. Hierarchical multiple regression analyses were used to determine the independent contribution of IED features on intellectual functioning, after controlling for effects of lesional pathology, epilepsy duration and medication. Exploratory analyses were conducted for language and memory scores as well as academic skills available in a subset of participants.

Results: The results reveal IED to have a negative association with IQ with independent, additive effects documented for frequent and bilaterally distributed IED as well as discharge enhancement in sleep. Left-lateralised IED had a prominent effect on verbal intelligence, in excess of the influence of left-sided brain pathology. These effects extended to other cognitive functions, most prominently for sleep enhanced IED to be associated with deficits in expressive and receptive language, reading, spelling and numerical skills.

Significance: Overall, IED effects were of a magnitude similar to lesional influences or drug effects (Topiramate use). This study demonstrates an association between IED and cognitive dysfunction, independent of the underlying focal brain pathology.

KEY WORDS: Focal epilepsy, children, interictal epileptiform discharges, cognition, intelligence

Introduction

Early onset childhood epilepsy is known to be associated with impaired cognitive development but the relationship of this to ongoing epileptiform activity remains controversial [1]. Interictal epileptiform discharges (IED) are sharp waves, spikes, or spike-wave complexes that occur in the absence of observable changes in behaviour [2]. A direct relationship between IED severity and the degree of short- and long-term cognitive impairment experienced by children with epilepsy has been suggested [3,4]. However, the debate continues as to whether IED are mainly an expression of the underlying brain pathology [4,5], a debate that extends to the question of whether pharmacological suppression of IED is warranted. Current evidence on the possible chronic impact of IED on cognition in children mainly derives from studies in patients with non-lesional epilepsy and with low seizure frequency [3,6,7].

Across studies in children with benign rolandic epilepsy (BRE) there is evidence that frequent and multifocal IED are associated with cognitive deficits, ranging from general intellectual functions [8], educational progress [3] to affecting only specific cognitive domains [6,8,9]. There is variability to the extent to which IED during sleep are associated with cognition, ranging from negative findings [10] to reporting robust effects on reading and verbal IQ [11]. A large study of children with predominantly non-lesional epilepsy syndromes also reported correlation of diurnal IED load with specific functions, such as information processing speed and short-term memory [6].

There is also some evidence for a modest influence of the laterality or topography of discharges, with left-sided and temporal IED correlating with some verbal scores [8] and right-sided IED with visuo-spatial performance [6]. However, laterality effects have not always been observed [9,11].

One important caveat in assuming a causal relationship between cognitive dysfunction and IED stems from the possibility that cognitive deficits could be due to the underlying

genetic abnormality, as evidenced by increased incidence of reading and speech-sound disorders in siblings of children with BRE [12]. The debate concerning the independent contribution of IED to cognition could therefore be informed by an empirical investigation of patients with epilepsy as a consequence of focal brain pathology, without a suspected or known genetic origin.

In the present study we investigated the possible impact of IED features on cognitive functioning, while accounting for seizure variables and type, extent and location of lesional pathology. Our primary hypotheses focussed on intelligence scores from the Wechsler scales as a marker of general cognitive ability, which are standardised across age groups and well comparable across centres. Based on the reviewed evidence in children with non-lesional epilepsy, it was hypothesized that IED exert an independent negative effect on intellectual performance; with high frequency and bilateral IED yielding reduced IQ scores [8]. Further, we hypothesised that left lateralized IED would be associated with poorer verbal abilities [13,14], in particular with greater VIQ-PIQ discrepancy scores as a sensitive index of lateralised brain dysfunction in children [15]. Secondary hypotheses predicted similar associations with more specific cognitive domains, such as language, memory and educational attainments, in particular with reading skills [11].

Method

Study design and participant selection

We conducted a retrospective case note review of EEG telemetry, neuroimaging and neuropsychology data in a cohort of children with medication-resistant, predominantly lesional, focal epilepsy who were referred for diagnostic investigations for epilepsy surgery. We included consecutive epilepsy surgery candidates who had completed structural/ functional neuroimaging, neuropsychological and other diagnostic evaluations at our centre,

between 2005-2013. Reports from neuropsychological, neuroradiological and clinical EEG telemetry were accessed via an electronic database at Great Ormond Street Children's Hospital following permission by the hospital ethical review board. Seizure-related information (i.e. type, frequency, age at seizure onset, and duration of epilepsy) and current medications were also retrieved from patient records. Specific emphasis was placed on Topiramate use, as this has been associated with reduced intellectual functioning [16].

Investigations and outcome measures

Neuropsychology: The standard protocol included age-appropriate measures of intelligence (Wechsler Intelligence Scale for Children, WISC IV or III) and academic attainments (Wechsler Individual Achievement Test, WIAT-II and in a minority using its earlier UK version - the WORD/WOND). Estimates for verbal and non-verbal intelligence were derived from the verbal comprehension and perceptual reasoning indices of the WISC. Depending on location of pathology and level of functioning of the child, memory assessments (using the Children's Memory Scale, CMS) and a clinical language screen (Clinical Evaluation of Language Fundamentals, CELF IV) were also administered. In about half of children with IQ scores below 70, memory and language tests were not administered. Neuropsychological scores were obtained as close in time to the EEG recording as possible, which in the majority of cases took part within a few days/ weeks, but extending to months in some cases.

Neurophysiology: Video EEG telemetry was performed across a median of 4 days and nights (range 1-5). Sleep was documented in 87/103 cases. The record was reviewed by one of four experienced paediatric neurophysiology consultants. The full report of ictal and interictal EEG features was evaluated. The background EEG was categorized into normal or abnormal, depending whether it fell within age-appropriate limits and it was noted if there were focal or generalized changes.

IED Frequency was classified categorically as 'none', 'rare/occasional/infrequent' and 'frequent'. By consensus between raters, 'frequent' discharges were denoted if the average number of IED was one or more per 10 second EEG epoch/page for the majority of the waking record. IED frequency was then categorised in a binary fashion as 'frequent' or 'infrequent' if this criterion was not met (see Refs. 6 and 7 for choice of the same criterion). Sleep-related IED enhancement was noted if there was a change in IED frequency category (increases or decreases, see above) from the waking state.

Neuroradiology: Detailed information about presence, extent and type of lesional pathology was derived from reports of a tailored epilepsy MRI protocol by a consultant paediatric neuroradiologist. A representative map of the distribution and type of focal lesions in half of the present cohort is shown elsewhere [17]. Lesion localisation was coded as frontal, temporal, parietal or other (multi-lobar, e.g. parieto-occipital).

Statistical Analysis

Pearson's correlation coefficient was calculated to assess the relationship between IQ and both age of onset and duration of epilepsy. Independent samples *t*-tests and analyses of variance (ANOVA) were used to investigate the effects of seizure, lesion and IED variables on IQ scores. Hierarchical regression analyses were performed to determine the independent contribution of IED variables on neuropsychological scores while controlling for relevant seizure and lesion-related variables. We examined inter-correlations to avoid significant associations between predictor variables, and tested the assumption of multicollinearity according to variance inflation factor values. Residual scatter plots were inspected for evidence of heteroscedacity. Statistical analyses were performed using IBM SPSS Statistics Version 21.

Results

Participants and sample characteristics

The current study was based on a cohort of 103 children with medication-resistant focal epilepsy who were undergoing assessment for epilepsy surgery at our centre (Table 1). The sample is characterised by a variety of generalised and focal seizure types. Three children previously presented with infantile spasms. Most patients (97%) were taking AEDs at the time of neuropsychological testing. Abnormalities on MRI were detected in 94% of cases and were more frequently lateralized to the left hemisphere (64%) and localized to the temporal lobes (36%). Twenty five children (24%) had intellectual disability as defined by an IQ score below 70.

Impact of seizure-related and lesional variables on intelligence scores

Lower IQ scores were associated with an earlier age of habitual seizure onset and longer duration of epilepsy (Table 2). These associations remained significant when patients with progressive (inflammatory) pathology were excluded (r=.31, p=.003; r=.40, p=.001, respectively). While there was no relationship of seizure frequency with IQ scores, there was some evidence that children with less severe seizures had better IQ scores. No clear association was found between IQ scores and number of AEDs administered at time of testing. However, Topiramate use was associated with an IQ decrement of about 10 points.

Among the MRI lesion variables, left-lateralised lesions were linked to a reduction in VIQ scores while patients with multilobar lesions, as compared to focal or no lesions had globally lower IQ scores. There was no IQ difference between cases with focal lesions and MRI-negative cases, nor between groups defined by the lesioned lobe (p>.372), when multilobar cases were excluded. There were also no significant interactions between lesion characteristics and any IED features, apart from a predicted association between lesion side and laterality of IED (χ^2=60.3, p<.0001).

Association between IED features and intelligence scores

The majority of children in this cohort (93%) showed IED in their EEG records. Children with frequent IED had lower IQ scores compared to children with infrequent or no IED (Table 2). A bilateral IED distribution (in 11% of cases) was associated with a reduction in PIQ compared to unilateral or no IED. Children with enhanced IED in sleep had reduced PIQ scores and showed a trend for lower VIQ scores (p=.087) compared to those without such increase. As predicted, children with IED recorded over the left hemisphere (or lateralised to the left side) showed a trend for lower VIQ scores (p=.061), and a much larger VIQ-PIQ discrepancy score (*mean*= -11, *SD*=12; *t(87)*=4.1, p<.001, *95% CI* [6-17]). There was no main effect of IED lobar scalp localization and of presence of abnormal EEG background activity on IQ scores.

Primary hypotheses: Independent contribution of IED variables to IQ scores

Hierarchical multiple regression analyses tested the contribution of IED, after controlling for the impact of seizure- and lesion-related variables (Model 1 in Table 2) which explained ~30% of the variance in IQ scores. Bilaterally distributed IED (compared to unilateral or no IED) accounted for a further 3-4% of IQ variance (Model 2). Frequent IED accounted for additional 5-6% (Model 3). Further IQ reduction was associated with enhanced IED occurrence in sleep (Model 4). The final models for each IQ measure included the following independent IED features: for VIQ – frequent and (in trend) sleep-enhanced IED; for PIQ – bilateral, frequent and sleep-enhanced IED.

Finally, a hierarchical regression analysis of VIQ-PIQ discrepancy scores after first accounting for presence of left-sided lesions (*F(1,87)*=6.81, p=.011), showed a major effect of left-lateralised IED (*F Change*=9.04, *df* =1,86, p=.003; β =-.410, p=.003), completely replacing the lesion effect (β =-.013, p=.927). When we evaluated if this association could be accounted for by the link with seizure onset from the left hemisphere (instead of IED

lateralization), no additional variance beyond lesion lateralisation was found (*F Change* =2.39, *df* =1,84, *p*=.126).

Secondary hypotheses: Independent association of IED with specific cognitive skills

We further explored if the final model identified above for IQ scores could also explain variability in scores of processing speed, academic attainments, language skills and memory performance obtained from a large part of our cohort (Table 4). It is important to point out that language scores, verbal memory and academic attainments were positively correlated with IQ (all r >.50), hence a possible association with IED cannot be seen as independent of intellectual ability. While some of the effects of Topiramate use, lesion localisation, and epilepsy duration were replicated for most of those cognitive measures, the effects of IED features showed some selectivity, which could not be explained by the reduced sample size. For example, while no IED effect on processing speed was found, there were clear effects of sleep-related IED enhancements on academic attainments such as reading, spelling and numerical operations. Similarly, robust effects of sleep IED enhancement were found for expressive and receptive language skills, while no such association with verbal and visual memory was seen.

Discussion

Our study suggests that IED independently contribute to cognitive compromise in children with structural epilepsy and may even be as detrimental to cognitive development as the underlying brain pathology itself. Specifically, high frequency of IED occurrence, bilateral scalp distribution and enhancement of IED during sleep independently predicted cognitive compromise when lesion, AED and seizure variables were carefully controlled. Our findings are complementary to previous research in children with non-lesional epilepsy [3,6-8,11].

Moderate effects of underlying brain pathology were observed, including reduced VIQ in children with left-sided lesions and overall IQ reductions in children with multilobar pathology. Interestingly, the effect of left-lateralised IED distribution on VIQ-PIQ discrepancy scores was found to be far in excess of that of the underlying lateralised brain pathology, confirming previous research in non-lesional epilepsy [14]. IED and seizure frequency were correlated; however we failed to find any association between seizure frequency and IQ scores, as in previous studies [6,7,11].

We assume that for the majority of patients in this cohort seizures were the consequence of focal lesional pathology. This is supported by a high rate of seizure freedom (~70%) at long-term post-operative follow-up currently under way. The fact that we observed an independent contribution from IED to IQ supports the hypothesis of a causative role of IED in contributing to cognitive dysfunction, extending the concept of 'epileptic encephalopathy' [18] to other forms of epilepsy [19].

We also confirmed the negative association of earlier age at epilepsy onset with IQ scores consistently reported in medication-resistant cohorts [20-24], highlighting the detrimental effect of early onset epilepsy on emerging cognitive networks. We did not find a significant

impact of number of AED used on cognitive functions, in agreement with a previous report [11], apart from the suspected negative effect of Topiramate [16].

Enhancement of epileptiform discharges in sleep has previously been associated with educational and behavioural impairments [3]. A detailed analysis by Ebus and colleagues [6] found only a partial effect of IED frequency in sleep on cognitive processing speed. This is congruent with the lack of IED effects on processing speed documented in our study. In contrast, robust sleep IED effects were found here for scores of oral language, reading, spelling and numerical operations. This supports findings in children with BRE showing a correlation of nocturnal (but not diurnal) IED frequency with reading scores [11]. Development of these skills across childhood is aided by sleep-dependent consolidation [25] and is therefore susceptible to chronic IED-related disruption [26,27]. In contrast, the lack of an IED correlation with memory retention over a short waking period was not surprising; given that we were not able to quantify discharge load and location during the neuropsychological testing period. Such short-term effects on memory have been shown when IED were quantified from hippocampal recordings during memory retention and recall [28], in analogy to effects of scalp-recorded IED on verbal and non-verbal tasks performance [13].

The retrospective case note review and cross-sectional nature are restrictions of our study design. A major limitation is the dichotomisation of IED frequency, used here to standardise this variable across telemetry EEG reports from different reviewers. Nevertheless, the cut-off of about 10% of the EEG record (i.e. >=1 IED per 10s epoch) for the high discharge frequency category used here corresponds to the threshold at which previous studies reported significant cognitive effects when seen in wakefulness [6,7] and sleep [11]. This dichotomisation nevertheless captures the inverse relationship observed between IED discharge frequency in sleep and memory retention in a recent quantitative study conducted in a comparable sample of surgical candidates at our centre [29], confirming a previous report

[26]. Although a further limitation could be the mix of pathologies included in this study, it enabled us to detect a significant impact of lesional pathology on IQ and to show robust independent IED effects. Finally, in the absence of longitudinal EEG recordings it is impossible to accurately estimate the chronic IED burden in our sample, as fluctuations can occur over longer time periods [30].

It remains currently unresolved which aetiological factors are responsible for the widely reported negative impact of longer illness duration on IQ [22,23], which was also observed here. Current best evidence on the long-term impact of static, early acquired brain lesions shows children only deviate from a normal cognitive trajectory if they also have epilepsy [31]. Conversely, selective recovery of VIQ scores seen after left temporal epilepsy surgery strongly suggests that, despite the surgical 'lesion', it is the cessation of seizure activity which is ultimately beneficial for cognition [16].

In conclusion, our study adds to the growing body of evidence suggesting that chronic exposure to frequent or bilateral IED during wakefulness and enhancement of discharges from wakefulness to sleep may have detrimental effects on cognitive development. Unlike previous studies, we have shown that IED have an association with cognition independent of the underlying brain pathology.

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Disclosures

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

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Key Points

- Lesional, drug and duration of epilepsy effects on cognitive scores were controlled for in hierarchical regression analyses.
- IQ decrement was independently associated with frequent IED (>=1/10s epoch) and bilaterally distributed IED.
- VIQ-PIQ discrepancy scores were related to left-sided IED in excess of effects of left hemisphere lesional pathology.
- Enhancement of IED from waking to sleep was associated with additional IQ decrements and deficits in academic and language skills.

Table 1

Sample Characteristics

Demographics and clinical variables	**Mean (SD)**
Gender (M/F)	49/54
Age (years)	12.7 (2.7)
Age at seizure onset (years)	6.2 (3.7)
Duration of epilepsy (years)	6.5 (4.0)
Seizure frequency (number/week)	7 (157)
Number of AEDs (median, range)	2 (0-5)
Verbal IQ	85 (18)
Performance IQ	87 (18)
Lesional Pathology	**n (%)**
MRI lesion negative	6 (6%)
Inflammatory	8 (8%)
Tumour*	27 (26%)
Atrophy	14 (14%)
MTS	15 (15%)
Malformations of cortical development	28 (27%)
Other**	5 (5%)
IED/ EEG Features	
Frequency (none/ infrequent/ frequent)	9/ 68/ 27
Laterality (L/ R/ Bilateral)	57/ 26/ 11
Lobe (F/ T/ F-T/ Other)	20/ 38/ 12/ 24
Sleep changes (fewer/ no change/ more)	15/ 20/ 49
Background EEG (normal/ mild/ abnormal)	35/ 28/ 40

* denotes dysembryoplastic neuroepithelial tumours (DNT), ** includes: white matter hyperintensive lesions, grey/white matter blurring, neurocutaneous melanosis, F – frontal, T- temporal, - F-T – fronto-temporal. MTS – mesial temporal sclerosis.

Table 2

Relationship of clinical, lesional and EEG/IED characteristics to IQ scores

Clinical variables	**Verbal IQ**	**Performance IQ**
Age at seizure onset (Pearson's R)	.15	.28**
Duration of epilepsy (Pearson's R)	-.21*	-.31**
Seizure frequency (Spearman's Rho)	.03	.07
Seizure type (aura/absence/dyscogn. vs. other)	+6.2 (4.2)	+11.0 (3.9)**
Number of AEDs (>2 vs. less)	-4.8 (3.8)	-.8 (3.7)
Topiramate (yes vs. no)	-10.7 (4.5)*	-10.9 (4.3)*
Lesional Pathology		
MRI Lesions: Left vs. Right	-10.3 (4.1)*	-4.1 (4.0)
Multi- vs. unilobar/other	-16.0 (3.7)***	-15.2 (3.5)***
IED/ EEG Features		
Frequency (frequent vs. infrequent/none)	-10.6 (3.9)**	-10.6(3.8)**
Laterality (bilateral vs. unilateral/none)	-10.7 (6.0)	-10.3 (4.5)*
Laterality (left-lateralised vs. other)	-7.0 (3.7)	+2.2 (3.7)
Sleep (enhanced vs. no change/less)	-7.1 (4.0)	-8.2 (3.8)*
Background EEG (abnormal vs. normal)	-4.0 (3.8)	-2.6 (4.0)

Legend: Table shows difference in IQ scores between contrasts indicated in left column (standard error in brackets), unless stated.

*p < .05, **p < .01, ***p < .001; comparisons marked with ** and *** survived Bonferroni correction for multiple comparisons.

Table 3

Hierarchical Multiple Regression Analyses of Intelligence Scores

	Model 1a (*n*=96)			Model 2a (*n*=88)			Model 3a (*n*=85)			Model 4a (*n*=74)		
Verbal IQ	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*
Topiramate use	-12.46	3.95	-.28**	-13.58	4.11	-.32**	-11.56	4.02	-.28**	-14.33	4.58	-.32**
Multi-lobar lesion localisation	-13.55	3.45	-.36***	-11.32	3.59	-.30**	-10.71	3.46	-.29**	-10.42	3.70	-.27**
Left lateralised lesions	-7.71	3.30	-.21*	-10.24	3.49	-.28**	-8.33	3.40	-.23*	-11.06	3.56	-.30**
Duration of epilepsy	-.86	.40	-.19*	-.68	.42	-.15	-.91	.42	-.21*	-.91	.44	-.20*
Bilateral IED				-10.64	5.49	-.18	-7.24	5.62	-.12	-7.92	5.59	-.14
Frequent IED							-8.80	3.57	-.24*	-8.53	3.81	-.23*
Sleep enhanced IED										-7.13	3.59	-.19(*)
R^2		.290			.311			.342			.437	
Adjusted R^2		.259			.269			.292			.377	
ΔR^2		.290			.032			.051			.034	
F Change		9.298***			3.75			6.087*			3.947(*)	
	Model 1b (*n*=98)			Model 2b (*n*=90)			Model 3b (*n*=86)			Model 4b (*n*=75)		
Performance IQ	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*
Topiramate use	-13.37	3.87	-.30**	-15.59	4.11	-.35***	-13.97	3.89	-.34**	-14.84	4.10	-.33**
Multi-lobar lesion localisation	-13.30	3.38	-.35***	-11.99	3.51	-.31**	-12.50	3.31	-.33***	-13.17	3.27	-.35***
Left lateralised lesions	-2.65	3.23	-.07	-4.76	3.42	-.13	-2.33	3.26	-.06	-3.08	3.16	-.08
Duration of epilepsy	-1.37	.39	-.31**	-1.37	.42	-.30**	-1.60	.40	-.35***	-1.59	.39	-.35***
Bilateral IED				-12.21	5.27	-.21*	-10.47	5.20	-.18*	-11.53	4.79	-.21*
Frequent IED							-9.82	3.43	-.26**	-10.05	3.38	-.27**
Sleep enhanced IED										-6.44	3.22	-.18*
R^2		.312			.342			.424			.536	
Adjusted R^2		.282			.303			.380			.487	
ΔR^2		.312			.042			.060			.028	
F Change		10.525***			5.356*			8.210**			4.005*	

(*)p = .051, *p < .05, **p < .01, ***p < .001; factors marked with ** and *** survived Bonferroni correction for multiple comparisons.

Table 4

Hierarchical Multiple Regression Analyses of other neuropsychological scores

	PSI (*n*=74)			Reading (*n*=72)			Spelling (*n*=69)			Numerical (*n*=72)		
	B	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*
Topiramate use	-10.33	4.91	-.24*	-3.68	5.63	-.07	-6.03	5.18	-.13	-12.47	5.90	-.22*
Multi-lobar lesion localisation	-9.95	3.92	-.28*	-17.17	4.69	-.39*	-15.75	4.44	-.39***	-19.29	4.97	-.39***
Left lateralised lesions	.42	3.75	.01	-7.82	4.53	-.18	-5.76	4.25	-.15	-7.79	4.66	-.17
Duration of epilepsy	-1.35	.48	-.31**	-.75	.56	-.14	-.22	.52	-.05	-1.32	.58	-.23*
Frequent IED	-6.52	5.94	-.12	-6.63	4.79	-.15	-3.81	4.47	-.09	-7.84	4.98	-.16
Bilateral IED	-4.58	4.19	-.12	-8.66	7.32	-.13	-1.96	7.19	-.03	-5.30	6.86	-.08
Sleep enhanced IED	-.45	3.90	-.01	-10.03	4.66	-.24*	-9.66	4.28	-.26*	-12.30	4.79	-.26*
R^2		.260			.343			.320			.418	
Adjusted R^2		.181			.280			.251			.363	
F		3.31**			5.40***			4.63***			7.54***	
	CELF Expressive (*n*=50)			CELF Receptive (*n*=50)			CMS Verbal (*n*=54)			CMS Visual (*n*=57)		
	B	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*
Topiramate use	-16.14	6.30	-.32*	-23.26	5.42	-.50***	-18.09	6.39	-.39**	-14.53	7.89	-.27
Multi-lobar lesion localisation	-7.56	5.79	-.16	-5.79	4.92	-.14	-6.86	5.59	-.17	1.03	7.17	.02
Left lateralised lesions	-13.65	5.34	-.33*	-7.94	4.58	-.20	-5.99	5.24	-.16	8.83	6.77	.19
Duration of epilepsy	-.10	.65	-.02	-.23	.55	-.05	-.35	.63	-.07	-1.25	.84	-.21
Frequent IED	-10.88	5.82	-.23	-5.42	5.01	-.12	-6.31	5.40	-.16	6.56	7.10	.13
Bilateral IED	-18.41	7.76	-.29*	-10.80	6.68	-.18	-1.98	7.36	-.04	-1.29	10.06	-.02
Sleep enhanced IED	-12.54	5.06	-.30*	-16.60	4.34	-.43***	-6.63	4.92	-.18	1.79	6.47	.04
R^2		.452			.523			.310			.166	
Adjusted R^2		.359			.444			.198			.042	
F		4.83***			6.59***			2.76*			1.34	

PSI = Processing Speed Index (derived from the WISC test); CELF = Clinical Evaluation of Language Fundamentals; CMS = Children's Memory Scale. *p < .05, **p < .01, ***p < .001; factors marked with ** and *** survived Bonferroni correction for multiple comparisons.