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Fetal antiepileptic drug exposure and learning and memory functioning at 6 years of age: The NEAD prospective observational study

Morris J. Cohen [a,*], Kimford J. Meador [b], Ryan May [c], Hayley Loblein [c], Thomas Conrad [c], Gus A. Baker [d], Rebecca L. Bromley [e,f], Jill Clayton-Smith [e,f], Laura A. Kalayjian [g], Andres Kanner [h], Joyce D. Liporace [i], Page B. Pennell [j], Michael Privitera [k], David W. Loring [l],for the NEAD Study Group

[a] Pediatric Neuropsychology International, Augusta, GA, United States of America
[b] Neurology & Neurological Sciences, Stanford University, Stanford, CA, United States of America
[c] EMMES Corp., Rockville, MD, United States of America
[d] Neurological Science, University of Liverpool, Merseyside, UK
[e] Manchester University Hospitals NHS Trust, Manchester, UK
[f] Division of Evolution and Genomic Science, School of Biological Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[g] University of Southern California, Los Angeles, CA, United States of America
[h] Neurology, University of Miami, Miami, FL, United States of America
[i] Great Valley Neurological Associates, Paoli, PA, United States of America
[j] Neurology, Harvard University, Boston, MA, United States of America
[k] Neurology, University of Cincinnati, Cincinnati, OH, United States of America
[l] Neurology, Emory University, Atlanta, GA, United States of America

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ABSTRACT

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study was a prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy on antiepileptic drug (AED) monotherapy from 1999 to 2004. The study aimed to determine if differential long-term neurodevelopmental effects exist across four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, and valproate). In this report, we examine fetal AED exposure effects on learning and memory functions in 221 six-year-old children (including four sets of twins) whose mothers took one of these AEDs during pregnancy. Their performance was compared with that of a national sample of normally developing six year olds from the standardization sample of the Children's Memory Scale (CMS). The major results of this study indicate that the mean performance levels of children exposed to valproate were significantly below that of the children in the normal comparison group across all seven of the CMS Indexes. With one exception, this finding held up at the subtest level as well. These findings taken together with nonsignificant verbal and nonverbal forgetting scores appear to indicate that, as a group, children exposed to valproate experienced significant difficulty in their ability to process, encode, and learn both auditory/verbal as well as visual/nonverbal material. In addition, they exhibited significant difficulty holding and manipulating information in immediate auditory working memory. However, once the information was learned and stored, the valproate-exposed children appeared to be able to retrieve the information they did learn at normal levels. Finally, the processing, working memory, and learning deficits demonstrated by the valproate-exposed children are dose-related. In contrast to valproate, the findings pertaining to the children exposed to carbamazepine, lamotrigine, and phenytoin in monotherapy are less clear. Therefore, further research will be required to delineate the potential risks to learning and memory functions in children exposed to carbamazepine, lamotrigine, and phenytoin in monotherapy during pregnancy. Additional research employing larger prospective studies will be required to confirm the long-term cognitive and behavioral risks to children of mothers who are prescribed these four AEDs during pregnancy as well as to delineate any potential risks of newer AEDs and to understand the underlying mechanisms of adverse AED effects on the immature brain.

1. Introduction

Animal studies have demonstrated that fetal exposure to some antiepileptic drugs (AEDs) at doses lower than those that result in structural

* Corresponding author at: Pediatric Neuropsychology International, 2963 Foxhall Circle, Augusta, GA 30907, United States of America.
E-mail address: mcohen@augusta.edu (M.J. Cohen).

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malformations can produce cognitive and behavioral deficits, alter neurochemistry, and reduce brain weight [1,2]. Further, AEDs including clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, and valproate can produce widespread neuronal apoptosis similar to alcohol in the immature rat brain [3–9]. This effect is dose-dependent, occurs at therapeutically relevant blood levels, requires only relatively brief exposure (single injection), and has been related to reduced expression of neurotrophins and levels of protein kinases that promote neuronal growth and survival. In addition, fetal alcohol exposure produces neuronal apoptosis and also results in impaired synaptic function in surviving neurons. Thus, it is likely that fetal exposure to certain AEDs may also impair synaptic function, which would impact learning and memory.

These observations suggest that certain AEDs might produce similar adverse effects in children exposed in utero or in the neonatal period. In fact, several AEDs have been associated with increased risk of major congenital malformations [10,11] and reduced cognitive abilities (e.g., intelligence quotient [IQ]) in children exposed in utero [12–16]. Further, in the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) follow-up study at 3 years of age [15], fetal valproate exposure was also shown to significantly impair verbal as well as nonverbal abilities, whereas carbamazepine significantly impacted only verbal abilities. In addition, there were dose-dependent relationships between both lower verbal and nonverbal abilities and higher valproate dose and between lower verbal abilities and higher carbamazepine dose. Six-year cognitive outcomes reported by the NEAD study group [17] indicated that children with fetal valproate exposure continued to exhibit significantly lower IQ than children exposed to carbamazepine, lamotrigine, or phenytoin. In addition, valproate-exposed children performed more poorly than the other three AEDs on measures of linguistic functioning and a global measure of learning/memory. Only higher valproate dose continued to be negatively associated with performance on measures of intelligence, linguistic functions, nonverbal abilities, a global measure of learning/memory, and executive functions. Further, children exposed to preconception folate exhibited higher mean IQ scores. Finally, in a more recent prospective analysis from the UK, which included the UK children from the NEAD study and a normally developing control group [18], six-year-old children exposed to high dosages of valproate (>800 mg daily) exhibited significantly lower full scale IQ (FSIQ) scores with a similar effect reported for verbal, nonverbal, and spatial abilities. Children exposed to high dose valproate also demonstrated an 8-fold increased need for educational intervention relative to controls. In contrast, children exposed in utero to carbamazepine or lamotrigine did not exhibit a significantly lower FSIQ; however, carbamazepine exposure resulted in significantly reduced verbal abilities.

As stated above, the NEAD Study Group [17], previously reported that the six-year-old cohort of valproate-exposed children performed more poorly than the other three AED groups on the Children's Memory Scale (CMS) General Memory Index (a measure of global learning/memory performance). As a result, the focus of this paper was a more detailed examination of the learning and memory functions of the NEAD study children at 6 years of age (final time point of the study) compared with that of a national sample of normally developing six-year-old children (normal comparison group) from the CMS standardization sample.

2. Methods

2.1. Design

The NEAD study was a prospective observational investigation with blinded assessments that examined the possible cognitive and behavioral teratogenesis of AEDs. Pregnant women with epilepsy on one of four AED monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate), were enrolled from October 1999 through February 2004 across 25 epilepsy centers in the USA and UK. During the enrollment period, no other AEDs were prescribed in adequate numbers to allow study. Polytherapy was not included because of its association with poorer outcomes [19]. A nonexposed control group was removed from the study's original design in accordance with the unanimous recommendation of the US National Institutes of Health review panel. This study is registered at clinicaltrials.gov as NCT00021866.

2.2. Participants

Institutional Review Boards at each center approved the study. Written informed consent for participation was obtained according to the Declaration of Helsinki. A National Institute of Health Data Safety Monitoring Board monitored study conduct and safety. Pregnant women with epilepsy on carbamazepine, lamotrigine, phenytoin, or valproate monotherapy were enrolled. Mothers with IQ below 70 were excluded to avoid floor effects because maternal IQ is the major predictor of child IQ in population studies [20]. Other exclusion criteria included positive syphilis or human immunodeficiency virus (HIV) serology, progressive cerebral disease, other major disease (e.g., diabetes), exposure to known teratogenic agents other than AEDs, poor AED compliance, drug misuse in the previous year, or sequelae of drug misuse. In order to obtain a normally developing comparison group for statistical analysis, the authors elected to include demographic and test data from the 100 children (50 male, 50 female) comprising the six-year-old normative sample from the CMS, with permission from The Psychological Corporation Pearson.

2.3. Procedure

For NEAD participants, information was collected (via questionnaires and medical record review) on potentially confounding variables, including maternal IQ; age; education; employment; race/ethnicity; seizure/epilepsy types and frequency; AED dosages; compliance; socioeconomic status [21]; UK/USA site; preconception and pregnancy folate use; use of alcohol, tobacco, or other drugs during pregnancy; unwanted pregnancy; abnormalities or complications in the present pregnancy or prior pregnancies; age at enrollment and birth; birth weight; childhood medical diseases; and breastfeeding. Children were classified as breastfed if they were currently breastfeeding at the time of the 3-month follow-up phone call after delivery. Because separate investigations with similar research designs in the US and UK were merged after the investigations were initiated, maternal IQs were assessed using different measures. These measures included the Test of Nonverbal Intelligence-3rd Edition (TONI-3) [22] in 267 mothers, the Wechsler Abbreviated Scale of Intelligence (WASI) [23] in 20 mothers, and the National Adult Reading Test (NART) [24] in 17 mothers. To allow for comparisons across AEDs, the dosages were standardized. Average AED dose during pregnancy was standardized relative to ranges observed within each group by the following calculation: $100 \times (\text{observed dose} - \text{minimum dose}) \div \text{range of doses}$.

For participants in the normal comparison group, information was collected on sex, race/ethnicity, and maternal education as part of the CMS standardization procedure. In addition, children included in the CMS standardization sample were all reading on grade level without a history of grade retention, referral for or placement within a special education program, and they were all free of neurological disorder (i.e., traumatic brain injury, seizures, brain tumor, cerebral palsy, neurocutaneous syndrome, or Tourette's syndrome).

In order to assess learning and memory functions, NEAD study children were administered the CMS [25] as part of the six-year-old neuropsychological assessment. The CMS assesses declarative learning and memory functions across three domains: Attention/Concentration, Auditory/Verbal, and Visual/Nonverbal. Each domain contains two core subtests and one supplemental subtest. The core subtests were administered for the purposes of this investigation. The subtests comprising the Attention/Concentration domain provide measures of focused attention and working memory. Each subtest in the Auditory/

Verbal and Visual/Nonverbal domains provide measures of both immediate and delayed (25–35 min) recall. Each Auditory/Verbal subtest also provides a measure of delayed recognition recall. Administration of the core subtests allows the examiner to derive eight index scores (mean = 100; standard deviation (sd) = 15): Attention/Concentration, Verbal Immediate, Verbal Delayed, Delayed Recognition, Visual Immediate, Visual Delayed, Learning, and General Memory. It should be noted that the Learning Index is derived using subtest scores from both the Auditory/Verbal (Word Pairs) and the Visual/Nonverbal (Dot Locations) domains. The General Memory Index is a measure of global memory functioning and is generated using both the immediate and delayed memory indexes from the Auditory/Verbal and Visual/Nonverbal domains. The results of AED group performance using the General Memory Index were previously reported by the NEAD study group [17] and as a result will not be a focus of this report.

The Attention/Concentration Index includes two subtests: Numbers and Sequences. Numbers is further subdivided into two components. Numbers forwards requires verbatim repetition of a string of numbers of gradually increasing length. Numbers Backward requires saying a string of numbers of gradually increasing length in reverse order. Sequences require mentally sequencing various rote sequences as quickly as possible. Items start out simple and become gradually more challenging. For example, reciting strings of numbers (e.g., count from 1 to 20), days of the week, or months of the year in forward order, to saying them in reverse order, to counting by a set amount (e.g., 2 s, 4 s, 6 s), to alternating between letters and numbers in order on the final item.

The core subtests comprising the Verbal Immediate, Verbal Delayed, and Delayed Recognition Indexes include Stories and Word Pairs. For Stories, children are required to listen to and immediately repeat a story read to them by the examiner. The story content does not need to be recalled in order for the child to obtain credit. There are 2 stories provided at each of three age levels. The delayed recall trial is also conducted in a free recall format and is immediately followed by a recognition trial in which the child is asked to answer questions related to each story in a "yes/no" format. For Word Pairs, children have to learn a list of 10 or 14 word pairs (10 for children six years of age) over three structured learning trials. Some paired associates are semantically related, but most are not. During each learning trial, the examiner reads the list, and then the child has to say the associate that goes with the stem provided by the examiner. Immediately following the three learning trials there is a free recall trial in which the child is asked to spontaneously provide as many of the word pairs as possible; the pairs can be said in any order. The delayed recall trial is presented in a free recall format as well. This is followed immediately by a recognition trial in which the children are asked to identify the word pairs mixed with foils in a "yes/no" format.

The core Visual Immediate and Visual Delayed subtests include Faces and Dot Locations. During the Faces Immediate subtest children are presented with a series of 12 or 16 human faces (12 for children six years of age) one at a time for 2 s each. Next, they are presented with 36 or 48 faces one at a time (36 for children six years of age) and they have to say whether or not each face was one of the original target faces presented. They have to do the same thing for the delayed recall portion; however, the foils are different so as to avoid confusion with those included in the immediate recall task. Hence, both immediate and delayed presentations use a recognition format. During the Dot Locations subtest, the children are presented with an array of 6 or 8 dots (6 for children six years of age) for 5 s. After the exposure, they have to immediately recall the location of the dots by placing chips on a grid. This is repeated for a total of three learning trials. After the learning trials the children are presented with a distractor trial (new array with different colored dots), followed by a short-delay recall trial of the original array. For the delayed recall subtest, the children are asked to demonstrate the location of the dots from the original array presented over the learning trials. Hence, Dot Locations uses a free recall format. The CMS possesses good psychometric properties, which are reported in the test manual.

Along with the CMS, all NEAD children were also administered the Differential Ability Scales (DAS) [26] as a measure of intelligence. A subset (38/100) of the six year olds in the CMS normative sample were also administered the Wechsler Intelligence Scale for Children, Third edition (WISC-III) [27] in order to develop a memory/IQ Linking Sample to provide CMS examiners with the ability to predict memory performance based upon a child's performance on IQ testing with the WISC-III. The correlation between the FSIQ score from the WISC-III and the General Cognitive Ability score from the DAS is high ($r = 0.92$) [27].

All NEAD study children were evaluated individually in accordance with the recommended administration procedures described in the CMS manual. All NEAD psychological examiners were blinded to drug group inclusion of the children they assessed. Training and monitoring of the neuropsychological evaluations were conducted to assure quality and consistency in test administration across all participating sites in the NEAD study. As part of this training, workshops were conducted for all neuropsychological test batteries annually. In addition, each NEAD examiner was required to identify errors and provide appropriate correction for videotaped testing sessions containing errors in administration and scoring. Examiners were also required to submit their own videotape of a practice test session (with a nonstudy child) with corresponding record forms to the Neuropsychology Core Director for review, feedback and approval. If examiners failed, they submitted additional video assessments for approval prior to testing study children. All test record forms completed on NEAD study children were rescored by the Neuropsychology Core to further minimize scoring and tabulation errors. Similar training and monitoring procedures were employed during data collection for the CMS standardization sample.

2.4. Data analysis

The primary analysis in this study included 221 children (four sets of twins) who were administered the CMS as part of the NEAD six-year-old neuropsychological assessment along with the 100 normally developing six-year-old children included in the normative sample from the CMS. Outcome data were missing for 90 children of the 305 NEAD study mothers who continued their enrollment in the study. Multivariate analysis of variance was used to examine differences between the CMS normative sample and each NEAD AED group, adjusting for covariates. Covariates included in each model were specific AED group (each of four AEDs and CMS), race (categorized as Caucasian/Black/Hispanic/Other), maternal education (categorized as high school or less/13–15 years/and 16+ years), and sex. Maternal education level was included as a substitute for maternal IQ (considered a stronger correlate with child index scores) because maternal IQ was not collected as part of the standardization procedure for the CMS. Gestational age at birth was also excluded as a covariate because it was not collected as part of the CMS. The specific dependent variables were child IQ (DAS GCA for NEAD study children and WISC-III FSIQ for children in the CMS standardization), and the child's performance on the seven CMS Index scores (Standard Score; mean = 100, sd = 15). The number of children with clinically at-risk scores (defined as 1.5 standard deviations below the mean standard score of 100) for each index were tabulated and compared with that of the CMS normative sample. Secondary analyses examined performance on the individual CMS subtest scores that comprised the seven Index scores (Scaled Score; mean = 10, standard deviation = 3). To determine if dose-dependent performance effects were present within the AED groups, Pearson correlations were computed for each of the CMS Indexes. Reported p-values are nominal and were not adjusted for multiple comparisons because of the exploratory nature of the study. Analyses were performed at the NEAD Data and Statistical Center using SAS statistical software and R software (www.R-project.org).

Table 1
IQ and demographics for mothers of NEAD children with and without CMS index observations.

	Mothers with at least one child's CMS indices observed (N = 217)	Mothers without at least one child's CMS indices observed (N = 88[a])	p-Value[b]
Continuous outcomes — mean (95% CI)			
Mean maternal IQ	98.9 (96.7, 101)	95.4 (92.1, 98.8)	0.0974
Mean gestational age in weeks	39.1 (38.8, 39.3)	38.5 (37.9, 39.1)	0.0845
Mean standardized dose	34.1 (31.4, 36.7)	36.3 (31.6, 40.9)	0.3965
Mean maternal age	30.3 (29.6, 31.0)	28.7 (27.4, 30.0)	0.0284
Categorical outcomes — n (%)			
Preconception folate	129 (59%)	45 (51%)	0.2028
Alcohol use during pregnancy	16 (7%)	8 (9%)	0.6413
Tobacco use during pregnancy	23 (11%)	14 (16%)	0.2447
Employed at time of enrollment	136 (63%)	54 (61%)	0.8964
Enrolled at site in the UK	89 (41%)	16 (18%)	0.0001
Epilepsy types			0.1922
Localization related	129 (59%)	55 (63%)	
Idiopathic generalized	67 (31%)	30 (34%)	
Generalized tonic–clonic	21 (10%)	3 (3%)	
Race			0.0405
Caucasian	183 (84%)	62 (70%)	
Black	7 (3%)	7 (8%)	
Hispanic	18 (8%)	13 (15%)	
Others	9 (4%)	6 (7%)	
Maternal education in years			0.2825
HS or less	88 (41%)	37 (43%)	
13–15	48 (22%)	25 (29%)	
16+	81 (37%)	25 (29%)	

[a] One mother in this group was missing a recorded educational level.
[b] p-Values were computed using *t*-tests for continuous variables and Fisher exact tests for categorical variables.

3. Results

Baseline maternal demographic characteristics of the 221 children (4 sets of twins) who were administered the CMS are depicted in Table 1. This table also shows a comparison of these demographic characteristics with the 88 mothers of children who were excluded from the analysis because of missing data. Mothers of children with missing CMS testing, who were excluded from analysis, differed statistically from mothers of children who were included on the following: maternal age (slightly younger), site location (UK sites had better retention), and racial/ethnic composition.

3.1. Demographic and child IQ group comparisons

Table 2 presents a comparison between the four AED groups and the normal control group on the three demographic variables that were collected on all groups. Table 3 presents adjusted group mean IQ scores along with the corresponding 95% confidence intervals. Consistent with previous NEAD study reports that compared the four AED groups with each other [14,16,17], the mean IQ of children whose mothers took valproate was found to be significantly lower ($p < 0.0001$) than the mean IQ of children in the normal control group. In addition, the mean IQ of children in the carbamazepine group was also significantly ($p < 0.04$) lower than that of the control group. Finally, as previously reported [17,18], Pearson correlations once again revealed a negative dose-dependent effect ($r = -0.45$; $p = 0.001$) for valproate but not for the other AEDs (See Fig. 1).

Table 3
AED effects on standardized mean age of 6 years IQ relative to a subset of the CMS normative sample.

AED	N	Standardized mean IQ (95% CI)[a]	Effect (95% CI)	p-Value
CBZ	61	106.2 (103.1, 109.3)	−5.4 (−10.4, −0.4)	0.0370
LTG	73	108.4 (105.5, 111.3)	−3.2 (−8.1, 1.8)	0.2111
PHT	39	107.4 (103.3, 111.4)	−4.2 (−9.8, 1.4)	0.1467
VPA	48	100.8 (97.2, 104.3)	−10.8 (−16, −5.6)	<0.0001
CMS	38	111.5 (107.6, 115.5)	reference	

[a] Standardized scores used: mean 100, sd 15.

3.2. CMS index comparisons

Statistical results, analyzing adjusted mean score performance across the seven CMS Index scores, are presented in Table 4. Results of the analysis of covariance model depicted in Table 4 indicate that although AED group means were in the average range, the performance of children exposed to valproate was significantly below that of the children in the normal comparison group across all seven of the CMS Indexes, with mean performance differences ranging from 7 to 14 points across the Indexes. Children exposed to lamotrigine performed significantly below the normal comparison group on the Attention/Concentration and Learning Indexes. Children in the carbamazepine-exposed group performed significantly below the normal comparison group on the Learning Index. Children in the phenytoin-exposed group performed significantly below the normal comparison group on the Learning and the Delayed Recognition Indexes.

In order to evaluate auditory/verbal and visual/nonverbal forgetting over the 25- to 35-minute interval between immediate and delayed spontaneous recall, analysis of covariance was performed on the difference scores between the delayed and immediate Verbal as well as Visual CMS Index scores. Table 5 presents the adjusted group mean difference scores and 95% confidence intervals. None of the AED groups exhibited verbal or visual forgetting scores that differed significantly from that of the normal comparison group. In order to determine if the AED groups exhibited significant modality specific performance differences, analysis

Table 2
Comparison of demographic variables — CMS normative sample vs. NEAD (All children with age of 6 years testing outcomes).

	CMS (N = 100) N (%)	CBZ (N = 61) N (%)	LTG (N = 73) N (%)	PHT (N = 39) N (%)	VPA (N = 48) N (%)	All NEAD (N = 221) N (%)	p-Value[1]
Sex							0.1322
Male	50 (50%)	24 (39%)	36 (49%)	18 (46%)	31 (65%)	109 (49%)	
Female	50 (50%)	37 (61%)	37 (51%)	21 (54%)	17 (35%)	112 (51%)	
Maternal education							0.0024
HS or less	46 (46%)	23 (38%)	20 (27%)	19 (49%)	28 (58%)	90 (41%)	
13–15 years	30 (30%)	14 (23%)	15 (21%)	8 (21%)	11 (23%)	48 (22%)	
16+ years	24 (24%)	24 (39%)	38 (52%)	12 (31%)	9 (19%)	83 (38%)	
Race							<0.0001
White	62 (62%)	54 (89%)	65 (89%)	24 (62%)	43 (90%)	186 (84%)	
Black	20 (20%)	2 (3%)	1 (1%)	3 (8%)	1 (2%)	7 (3%)	
Hispanic	12 (12%)	3 (5%)	3 (4%)	11 (28%)	2 (4%)	19 (9%)	
Other	6 (6%)	2 (3%)	4 (5%)	1 (3%)	2 (4%)	9 (4%)	

[a] p-Values were computed using chi-square tests for the CMS, CBZ, LTG, PHT, and VPA groups.

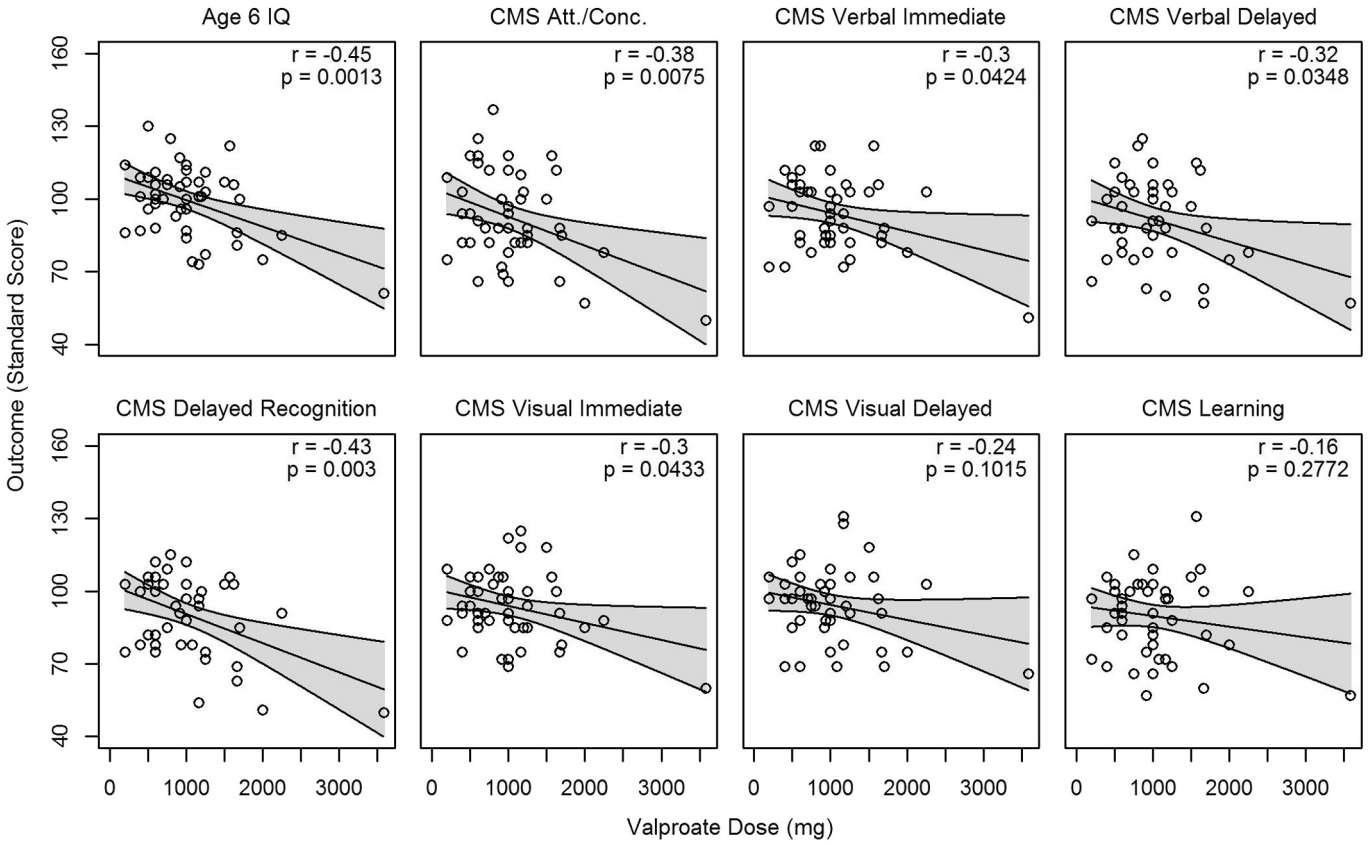

Fig. 1. Valproate dose effects for IQ and CMS indexes.

Table 4
AED effects on the standardized group mean performance levels on the seven CMS indexes relative to the CMS normative sample.

CMS index	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
Attention/concentration	CBZ	61	101.2 (96.8, 105.5)	−3.1 (−8.7, 2.6)	0.2852
	LTG	72	98.2 (94.2, 102.3)	−6 (−11.5, −0.5)	0.0321
	PHT	38	98 (92.5, 103.6)	−6.2 (−12.7, 0.3)	0.0628
	VPA	48	94.1 (89.1, 99.1)	−10.2 (−16.3, −4.1)	0.0012
	CMS	100	104.3 (100.8, 107.7)	reference	
Verbal immediate	CBZ	61	103.2 (99.4, 107)	−1.6 (−6.5, 3.3)	0.5119
	LTG	71	103.1 (99.6, 106.7)	−1.7 (−6.5, 3.1)	0.4846
	PHT	39	100.8 (96, 105.6)	−4 (−9.7, 1.6)	0.1588
	VPA	46	94.5 (90, 98.9)	−10.4 (−15.8, −5)	0.0002
	CMS	100	104.8 (101.8, 107.9)	reference	
Verbal delayed	CBZ	61	103.8 (99.5, 108.1)	0 (−5.6, 5.5)	0.9931
	LTG	71	103.6 (99.6, 107.6)	−0.3 (−5.6, 5.1)	0.9261
	PHT	39	99.1 (93.7, 104.5)	−4.8 (−11.1, 1.6)	0.1416
	VPA	45	92.2 (87.2, 97.3)	−11.6 (−17.7, −5.5)	0.0002
	CMS	100	103.8 (100.4, 107.3)	reference	
Delayed recognition	CBZ	60	101.5 (97.8, 105.2)	−3.8 (−8.6, 1)	0.1227
	LTG	72	103.1 (99.7, 106.6)	−2.2 (−6.8, 2.5)	0.3591
	PHT	39	99.3 (94.6, 103.9)	−6 (−11.5, −0.5)	0.0319
	VPA	45	90.4 (86, 94.7)	−14.9 (−20.2, −9.6)	<0.0001
	CMS	100	105.3 (102.3, 108.3)	reference	
Visual immediate	CBZ	61	98.6 (95, 102.1)	−3.1 (−7.7, 1.5)	0.1905
	LTG	73	100.6 (97.3, 103.9)	−1.1 (−5.6, 3.4)	0.6363
	PHT	39	97.3 (92.8, 101.8)	−4.4 (−9.7, 0.9)	0.1079
	VPA	47	94.4 (90.3, 98.5)	−7.3 (−12.3, −2.2)	0.0053
	CMS	100	101.7 (98.8, 104.5)	reference	
Visual delayed	CBZ	61	103.4 (99.7, 107)	0.2 (−4.5, 4.9)	0.9247
	LTG	73	105.3 (101.9, 108.7)	2.2 (−2.4, 6.7)	0.3555
	PHT	39	99.4 (94.8, 104.1)	−3.7 (−9.1, 1.7)	0.1789
	VPA	46	95.2 (90.9, 99.4)	−8 (−13.2, −2.8)	0.0028
	CMS	100	103.2 (100.2, 106.1)	reference	
Learning	CBZ	61	98.4 (94.6, 102.1)	−5.1 (−10, −0.3)	0.0388
	LTG	72	98 (94.5, 101.5)	−5.5 (−10.2, −0.8)	0.0218
	PHT	39	94.7 (89.9, 99.4)	−8.8 (−14.4, −3.3)	0.0020
	VPA	47	90.2 (85.9, 94.6)	−13.3 (−18.6, −8)	<0.0001
	CMS	100	103.5 (100.5, 106.5)	reference	

[a] Standardized scores used: mean 100, sd 15.

Table 5
AED effects on Auditory/Verbal and Visual/Nonverbal forgetting at the index level relative to the CMS normative sample.

CMS index	AED	N	Standardized mean difference (95% CI)[a]	Effect (95% CI)	p-Value
Verbal delayed minus verbal immediate	CBZ	61	0.6 (−2.2, 3.4)	1.6 (−2, 5.2)	0.3777
	LTG	71	0.4 (−2.2, 3)	1.4 (−2, 4.9)	0.4161
	PHT	39	−1.7 (−5.2, 1.8)	−0.7 (−4.8, 3.4)	0.7284
	VPA	45	−2.5 (−5.7, 0.8)	−1.5 (−5.4, 2.5)	0.4658
	CMS	100	−1 (−3.2, 1.2)	reference	
Visual delayed minus visual immediate	CBZ	61	4.8 (2.2, 7.5)	3.3 (−0.1, 6.8)	0.0577
	LTG	73	4.7 (2.3, 7.2)	3.2 (−0.1, 6.6)	0.0567
	PHT	39	2.1 (−1.2, 5.5)	0.7 (−3.3, 4.6)	0.7426
	VPA	46	0.9 (−2.2, 4)	−0.6 (−4.3, 3.2)	0.7706
	CMS	100	1.5 (−0.6, 3.6)	reference	

[a] Standardized scores have a mean of 100, sd 15. Differences between scores have a mean of 0, sd 21.

of covariance was carried out on the differences between the Verbal and Visual Immediate and the Verbal and Visual Delayed Indexes. Table 6 presents the adjusted group mean difference scores and 95% confidence intervals. None of the AED groups exhibited verbal–visual discrepancy scores that differed significantly from that of the normal comparison group.

Finally, in order to evaluate the impact of fetal AED exposure from a clinical perspective, Table 7 provides the frequency/percentage of children in each AED group who obtained an at-risk standard score, for each of the CMS Indexes, relative to the children in the CMS normative sample. An at-risk score was defined as being ≤77 (1.5 standard deviations below the mean of 100). Analysis of Table 7 indicates that children in the valproate group exhibited significantly higher percentages of clinically at-risk scores on six of the seven CMS Indexes, ranging from 11 to 23 percentage points across the Indexes.

3.3. CMS subtest comparisons

Given the significant performance decrements found at the index level for children who were exposed to valproate and to a much lesser degree for children exposed to the other AEDs, analyses were conducted in order to further explore AED group performance at the individual subtest level. Results of the analysis of covariance models for the CMS subtests are presented in Tables 8A through 8E.

Statistical results, analyzing adjusted mean score performance across the CMS subtests comprising the Attention/Concentration Index (Numbers and Sequences) are presented in Table 8A. Results of the analysis of covariance model indicate that across both subtests, the performance of children exposed to valproate was found to be significantly below that of the normal comparison group. No other AED group comparisons were significant. This finding appears to indicate that as a group, children exposed to valproate experienced more difficulty with focused attention and auditory/verbal working memory. Further, the significant result seen for lamotrigine at the Index level did not hold up at the subtest level.

Table 8B provides the results of analysis of covariance across the specific CMS scores derived from Stories and Word Pairs, which are the two subtests that make up the Verbal Immediate, Verbal Delayed, and Delayed Recognition Indexes as well as a portion of the Learning Index. Results of the analysis of covariance model indicate that the mean performance levels of children in the valproate group were significantly below that of the normal comparison group when they were asked to learn and recall meaningful/organized (Stories) as well as rote/unorganized (Word Pairs) verbal information immediately after

Table 6
AED effects on the Immediate and Delayed Modality specific performance differences relative to the CMS normative sample.

CMS index	AED	N	Standardized mean difference (95% CI)[a]	Effect (95% CI)	p-Value
Verbal immediate minus visual immediate	CBZ	61	4.6 (0.4, 8.9)	1.4 (−4, 6.9)	0.6054
	LTG	71	2.9 (−1.1, 6.9)	−0.3 (−5.6, 5)	0.9127
	PHT	39	3.5 (−1.9, 8.9)	0.3 (−6, 6.6)	0.9178
	VPA	46	0 (−4.9, 5)	−3.1 (−9.2, 2.9)	0.3092
	CMS	100	3.2 (−0.2, 6.6)	reference	
Verbal delayed minus visual delayed	CBZ	61	0.4 (−4.4, 5.2)	−0.3 (−6.5, 6)	0.9342
	LTG	71	−1.5 (−6, 3)	−2.2 (−8.3, 3.9)	0.4798
	PHT	39	−0.4 (−6.4, 5.7)	−1 (−8.2, 6.1)	0.7758
	VPA	45	−2.8 (−8.4, 2.9)	−3.4 (−10.3, 3.5)	0.3279
	CMS	100	0.7 (−3.2, 4.5)	reference	

[a] Standardized scores have a mean of 100, sd 15. Differences between scores have a mean of 0, sd 21.

Table 7
Frequency/percent of children by AED group with clinically at-risk CMS index scores relative to the CMS normative sample.

CMS index	Group index score frequencies (%) ≤77				
	CMS	VPA	CBZ	LTG	PHT
	n (%)	n (%)	n (%)	n (%)	n (%)
Attention/concentration index	6 (5.08)	8 (16.67)*	9 (14.75)*	8 (11.11)	5 (13.16)
Verbal immediate	4 (3.42)	5 (10.87)	3 (4.92)	2 (2.82)	4 (10.26)
Verbal delayed	3 (2.61)	9 (20.00)***	5 (8.20)	7 (9.86)*	7 (17.95)**
Delayed recognition	5 (4.24)	9 (20.00)**	5 (8.33)	3 (4.17)	4 (10.26)
Visual immediate	5 (4.27)	7 (14.89)*	4 (6.56)	3 (4.11)	2 (5.13)
Visual delayed	4 (3.39)	9 (19.57)**	3 (4.92)	2 (2.74)	1 (2.56)
Learning index	5 (4.24)	11 (23.40)***	5 (8.20)	5 (6.94)	4 (10.26)

Comparisons to CMS normative rates performed via Fishers Exact Test, with significance of unadjusted p-values reported at the following levels * = 0.05, ** = 0.01, *** = 0.001.

Table 8A
AED effects on the standardized group mean performance levels on the CMS subtests comprising the Attention/Concentration index relative to the CMS normative sample.

CMS subtest	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
Numbers total score	CBZ	61	10.4 (9.6, 11.2)	0.2 (−0.8, 1.2)	0.7323
	LTG	72	9.5 (8.8, 10.3)	−0.7 (−1.7, 0.3)	0.1636
	PHT	38	10 (9, 11)	−0.3 (−1.4, 0.9)	0.6651
	VPA	48	9.1 (8.2, 9.9)	−1.2 (−2.2, −0.1)	0.0349
	CMS	100	10.2 (9.6, 10.8)	reference	
Sequences total score	CBZ	61	9.7 (8.8, 10.6)	−0.6 (−1.8, 0.5)	0.2571
	LTG	72	9.6 (8.8, 10.4)	−0.8 (−1.9, 0.3)	0.1506
	PHT	39	9.9 (8.8, 11)	−0.4 (−1.7, 0.8)	0.5145
	VPA	48	8.8 (7.8, 9.8)	−1.6 (−2.8, −0.4)	0.0118
	CMS	100	10.3 (9.7, 11)	reference	

[a] Scaled scores used for subtests: mean 10, sd 3.

presentation as well as 25 to 35 min later. In addition, children in the lamotrigine group exhibited significantly lower verbal learning efficiency across the three learning trials of the Word Pairs subtest as compared with the normal comparison group. Finally, results presented in Table 8C indicate that none of the AED groups exhibited verbal forgetting scores that differed significantly from that of the normal comparison group.

Table 8D provides the results of analysis of covariance across the specific CMS subtests scores derived from Dot Locations and Faces, which are the two subtests that make up the Visual Immediate and Visual Delayed Indexes as well as a portion of the Learning Index. Results of the analysis of covariance model indicate that the mean performance levels of children in the valproate group were significantly below that of the normal comparison group when they were asked to learn and immediately recall the spatial location of an array of dots (where). However, the mean performance level for the valproate group improved and was no longer significantly below that of the normal comparison group at delayed recall. The mean performance level of children exposed to phenytoin was also significantly below that of the normal comparison group when they were asked to immediately recall spatial location. Further, it is Interesting to note that children exposed to carbamazepine and lamotrigine performed significantly above that of the normal comparison group at delayed recall for spatial location. When asked to recall a series of pictured human faces (what), children in the valproate group performed significantly below the normal comparison group immediately after presentation as well as 25 to 35 min later. Children exposed to carbamazepine performed significantly below the normal comparison group during immediate recall of faces but not at delayed recall.

Finally, the results presented in Table 8E indicate that consistent with the findings reported for Dot Locations delayed recall in Table 8D, the mean forgetting scores for children in the carbamazepine, lamotrigine, and phenytoin groups was actually significantly elevated (improved performance at delayed recall vs. immediate recall) as compared with that seen in the normal comparison group. However, on the Faces subtest, none of the AED groups exhibited nonverbal/visual forgetting scores that differed significantly from that of the normal comparison group.

Table 8B
AED effects on standardized group mean performance levels on the CMS subtests comprising the Auditory/Verbal Domain relative to the CMS normative sample.

CMS subtest	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
Stories					
Immediate recall	CBZ	61	10.8 (10, 11.5)	0.4 (−0.6, 1.3)	0.4618
	LTG	71	10.9 (10.2, 11.6)	0.5 (−0.4, 1.5)	0.2608
	PHT	39	10.6 (9.6, 11.5)	0.2 (−0.9, 1.3)	0.7202
	VPA	47	9.3 (8.4, 10.2)	−1.1 (−2.1, 0)	0.0455
	CMS	100	10.4 (9.8, 11)	reference	
Delayed recall	CBZ	61	10.6 (9.7, 11.4)	0 (−1, 1.1)	0.9818
	LTG	71	10.8 (10, 11.5)	0.2 (−0.8, 1.3)	0.6607
	PHT	39	10.3 (9.3, 11.3)	−0.3 (−1.5, 1)	0.6795
	VPA	47	8.9 (7.9, 9.8)	−1.7 (−2.8, −0.5)	0.0046
	CMS	100	10.5 (9.9, 11.2)	reference	
Delayed recognition	CBZ	60	10.2 (9.5, 10.9)	−0.1 (−1, 0.9)	0.9149
	LTG	72	10.3 (9.6, 11)	0.1 (−0.8, 1)	0.8411
	PHT	39	9.9 (9, 10.8)	−0.3 (−1.4, 0.7)	0.5426
	VPA	46	8.6 (7.7, 9.4)	−1.7 (−2.7, −0.6)	0.0017
	CMS	100	10.2 (9.7, 10.8)	reference	
Word pairs					
Total score	CBZ	61	10.1 (9.3, 10.9)	−0.3 (−1.3, 0.8)	0.6241
	LTG	72	10 (9.2, 10.7)	−0.4 (−1.4, 0.6)	0.4304
	PHT	39	9.9 (8.9, 10.9)	−0.4 (−1.6, 0.7)	0.4551
	VPA	47	8.5 (7.6, 9.4)	−1.9 (−3, −0.7)	0.0012
	CMS	100	10.4 (9.7, 11)	reference	
Long delay	CBZ	61	10.5 (9.6, 11.4)	0 (−1.1, 1.2)	0.9614
	LTG	72	10.2 (9.3, 11)	−0.3 (−1.4, 0.9)	0.6555
	PHT	39	9.6 (8.5, 10.8)	−0.8 (−2.1, 0.5)	0.2372
	VPA	46	8.4 (7.3, 9.4)	−2 (−3.3, −0.7)	0.0021
	CMS	100	10.4 (9.7, 11.1)	reference	
Delayed recognition	CBZ	60	10.3 (9.4, 11.1)	0.3 (−0.8, 1.4)	0.5957
	LTG	72	10.5 (9.7, 11.3)	0.5 (−0.5, 1.6)	0.3173
	PHT	39	10.1 (9.1, 11.2)	0.2 (−1.1, 1.4)	0.7952
	VPA	46	8.1 (7.1, 9)	−1.9 (−3.1, −0.7)	0.0020
	CMS	100	10 (9.3, 10.6)	reference	
Learning	CBZ	61	9.4 (8.6, 10.3)	−1 (−2.1, 0)	0.0564
	LTG	72	9.4 (8.7, 10.2)	−1.1 (−2.1, 0)	0.0440
	PHT	39	9.4 (8.4, 10.4)	−1.1 (−2.3, 0.1)	0.0856
	VPA	47	7.8 (6.9, 8.8)	−2.7 (−3.8, −1.5)	<0.0001
	CMS	100	10.5 (9.8, 11.1)	reference	

[a] Scaled scores used for subtests: mean 10, sd 3.

3.4. AED dose effects

Pearson correlations were computed for each of the CMS Indexes in order to determine if dose-dependent performance effects were present within each of the four AED drug groups. Significant negative effects were found for five of the seven CMS Indexes in the valproate-exposed group as depicted in Fig. 1. With the exception of the Verbal Immediate Index for the carbamazepine group ($r = -0.26$; $p = 0.04$) no other significant drug-dependent effects were present for any of the other AED groups.

4. Discussion

The NEAD Study is the largest prospective observational investigation of cognitive and behavioral outcomes following fetal exposure to valproate, carbamazepine, lamotrigine, and phenytoin in monotherapy. This study sought to determine if differential long-term neurodevelopmental effects exist across these four commonly used AEDs. In a previous report by the NEAD Study Group [17], the six-year-old cohort of valproate-exposed children performed more poorly, in comparison to children exposed to other AEDs, on the General Memory Index of the CMS, which is a global measure of learning/memory (differences ranging from 9 to 14 points). Given this finding, we elected to undertake a more detailed examination of the effects of fetal AED exposure on learning and memory functions in the NEAD Study children at six years of age, which was the end point of the study.

Table 8C
AED effects on Auditory/Verbal Forgetting at the subtest level relative to the CMS normative sample.

CMS subtest	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
	CBZ	61	−0.2 (−0.7, 0.3)	−0.4 (−0.9, 0.2)	0.2401
	LTG	71	−0.2 (−0.6, 0.3)	−0.3 (−0.9, 0.3)	0.2833
Stories: delayed recall minus immediate	PHT	39	−0.3 (−0.9, 0.3)	−0.5 (−1.1, 0.2)	0.1832
	VPA	47	−0.4 (−1, 0.1)	−0.6 (−1.2, 0.1)	0.0725
	CMS	100	0.2 (−0.2, 0.5)	reference	
	CBZ	61	−0.4 (−1.1, 0.4)	−0.1 (−1.1, 0.9)	0.9024
	LTG	71	−0.5 (−1.3, 0.2)	−0.2 (−1.2, 0.8)	0.6627
Stories: delayed recognition minus delayed recall	PHT	39	−0.4 (−1.4, 0.6)	−0.1 (−1.2, 1.1)	0.8849
	VPA	46	−0.3 (−1.2, 0.6)	0 (−1.1, 1.1)	0.9678
	CMS	100	−0.3 (−0.9, 0.3)	reference	
	CBZ	61	0.3 (−0.5, 1.2)	0.3 (−0.8, 1.3)	0.6050
	LTG	72	0.2 (−0.6, 1)	0.1 (−0.9, 1.2)	0.7911
Word pairs: long delay minus total score	PHT	39	−0.3 (−1.3, 0.7)	−0.4 (−1.6, 0.9)	0.5598
	VPA	46	−0.2 (−1.2, 0.8)	−0.3 (−1.4, 0.9)	0.6519
	CMS	100	0.1 (−0.6, 0.7)	reference	
	CBZ	60	−0.2 (−1.1, 0.7)	0.3 (−1, 1.5)	0.6676
	LTG	72	0.3 (−0.6, 1.2)	0.8 (−0.4, 2)	0.1870
Word pairs: delayed recognition minus long delay	PHT	39	0.5 (−0.7, 1.7)	1 (−0.4, 2.4)	0.1737
	VPA	46	−0.3 (−1.4, 0.8)	0.1 (−1.2, 1.5)	0.8550
	CMS	100	−0.5 (−1.2, 0.3)	reference	

[a] Scaled scores used for subtests: mean 10, sd 3.

Similar to the prospective findings reported by Baker, Bromley, Briggs, et al. [18], six-year-old children in the NEAD study, who were administered the CMS and exposed to valproate during fetal development, exhibited a significantly lower mean FSIQ score as compared with a subset of the normally developing six-year-old children in the CMS standardization sample. Further, as previously reported in the NEAD and UK studies [17,18], Pearson correlations revealed a significant negative dose-dependent performance effect for children exposed to valproate but not for the other AEDs. Thus, these findings lend further support for the contention that fetal exposure to valproate is associated with intellectual deficits, especially at increased dosages. Research into the intellectual effects of fetal exposure to carbamazepine is less clear.

Table 8D
AED effects on standardized group mean performance levels on the CMS subtests comprising the Visual/Nonverbal Domain relative to the CMS normative sample.

CMS subtest	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
Dot location					
	CBZ	61	10.4 (9.7, 11.2)	−0.1 (−1.1, 0.9)	0.8480
	LTG	73	10.5 (9.8, 11.2)	0 (−1, 0.9)	0.9542
Total score	PHT	39	9.4 (8.4, 10.3)	−1.1 (−2.3, 0)	0.0476
	VPA	48	9.4 (8.5, 10.2)	−1.2 (−2.2, −0.1)	0.0318
	CMS	100	10.5 (9.9, 11.1)	reference	
	CBZ	61	11.2 (10.5, 11.9)	1 (0, 1.9)	0.0395
	LTG	73	11.5 (10.8, 12.1)	1.2 (0.3, 2.1)	0.0068
Long delay	PHT	39	10.5 (9.6, 11.4)	0.2 (−0.8, 1.3)	0.6397
	VPA	48	10 (9.2, 10.8)	−0.3 (−1.2, 0.7)	0.5974
	CMS	100	10.3 (9.7, 10.8)	reference	
	CBZ	61	9.8 (9, 10.6)	−0.4 (−1.5, 0.6)	0.3862
	LTG	73	9.8 (9.1, 10.5)	−0.5 (−1.4, 0.5)	0.3536
Learning	PHT	39	9.1 (8.1, 10.1)	−1.1 (−2.3, 0)	0.0557
	VPA	48	8.7 (7.8, 9.6)	−1.5 (−2.6, −0.4)	0.0067
	CMS	100	10.3 (9.6, 10.9)	reference	
Faces					
	CBZ	61	9 (8.3, 9.8)	−1 (−2, 0)	0.0450
	LTG	73	9.6 (8.9, 10.3)	−0.5 (−1.4, 0.5)	0.3253
Immediate recall	PHT	39	9.7 (8.8, 10.7)	−0.3 (−1.4, 0.8)	0.5845
	VPA	47	8.8 (8, 9.7)	−1.2 (−2.3, −0.1)	0.0282
	CMS	99	10 (9.4, 10.6)	reference	
	CBZ	61	9.8 (9, 10.6)	−0.3 (−1.4, 0.7)	0.5670
	LTG	73	10 (9.3, 10.8)	−0.1 (−1.1, 0.9)	0.8639
Delayed recall	PHT	39	9.4 (8.4, 10.4)	−0.7 (−1.9, 0.5)	0.2432
	VPA	46	8.3 (7.3, 9.2)	−1.9 (−3, −0.7)	0.0020
	CMS	100	10.1 (9.5, 10.8)	reference	

[a] Scaled scores used for subtests: mean 10, sd 3.

While the mean FSIQ of children in the carbamazepine group was also significantly lower (to a lesser degree) than that of the normal developing six-year-old comparison group, this finding was not reported in the NEAD and UK studies [17,18] as well as a large Finnish study, which also reported normal intelligence scores for children prenatally exposed to carbamazepine [13]. Therefore, further research appears to be necessary in order to fully delineate the intellectual risk associated with fetal exposure to carbamazepine. Finally, children exposed to lamotrigine and phenytoin did not exhibit significant mean performance differences in FSIQ consistent with the findings reported in the NEAD and UK studies [17,18].

To date, the NEAD study is the first investigation, to undertake a comprehensive, prospective exploration of learning and memory functions in the children of mothers who were prescribed these four AEDs in monotherapy during their pregnancies. The major results of this study indicate that although adjusted mean scores for the four AED groups were in the average range across all of the Indexes and subtests comprising the CMS, the mean performance levels of children exposed to valproate were in the lower end of the normal range and significantly below that of the children in the normal comparison group across all seven of the CMS Indexes. With one exception, this finding held up at the subtest level. Further, significant negative dose-dependent performance effects were found at the Index level for children exposed to valproate. These findings taken together with nonsignificant verbal and nonverbal forgetting scores (25 to 35 min later) appear to indicate that, as a group, children exposed to valproate experienced significant difficulty in their ability to process, encode and learn both auditory/verbal as well as visual/nonverbal material. In addition, they exhibited significant difficulty holding and manipulating information in immediate working memory. However, once the information was learned and stored, the valproate-exposed children appeared to be able to retrieve the information they did learn at normal levels. Finally, the processing, working memory and learning deficits demonstrated by the valproate-exposed children are dose-related.

The current findings for valproate are consistent with what would be expected based upon the 6-year cognitive outcome data (intelligence, linguistic functions, nonverbal abilities, and executive functions) reported by the NEAD study group [17] as well as the fairly extensive literature investigating the learning and memory performance of children exposed to prenatal alcohol [28]. Together, these findings support the contention that the auditory/verbal and visual/nonverbal episodic memory deficits involving processing, encoding, and learning are being influenced by higher order cognitive processes. Further, the

Table 8E
AED Effects on Visual/Nonverbal Forgetting at the subtest level relative to the CMS normative sample.

CMS subtest	AED	N	Standardized mean (95% CI)[a]	Effect (95% CI)	p-Value
Dot location: long delay minus total score	CBZ	61	0.8 (0.1, 1.5)	1.1 (0.1, 2)	0.0274
	LTG	73	1 (0.3, 1.7)	1.2 (0.3, 2.1)	0.0071
	PHT	39	1.1 (0.2, 2)	1.4 (0.3, 2.5)	0.0108
	VPA	48	0.7 (−0.2, 1.5)	0.9 (−0.1, 1.9)	0.0772
	CMS	100	−0.3 (−0.8, 0.3)	reference	
Faces: delayed recall minus immediate recall	CBZ	61	0.8 (0.1, 1.5)	0.7 (−0.2, 1.6)	0.1060
	LTG	73	0.5 (−0.2, 1.1)	0.4 (−0.4, 1.3)	0.3426
	PHT	39	−0.3 (−1.2, 0.6)	−0.4 (−1.4, 0.6)	0.4770
	VPA	46	−0.6 (−1.4, 0.2)	−0.7 (−1.6, 0.3)	0.1756
	CMS	99	0.1 (−0.5, 0.6)	reference	

[a] Scaled scores used for subtests: mean 10, sd 3.

significant deficit in working memory seen only in the valproate group is a finding that is also frequently reported in studies of children diagnosed with attention-deficit/hyperactivity disorder (ADHD) [29]. It is interesting to note that this relationship would appear to be consistent with a previous report by the NEAD study group [30] that found a significant elevation in the percentage (21.4%) of six-year-old valproate-exposed children who were at significant risk for ADHD (based upon data from parent and teacher behavior rating scales). Finally, the magnitude of the performance discrepancies seen in the valproate-exposed children on measures of processing, learning, and working memory are likely to have a significant impact upon their academic and adaptive functioning and contribute to the elevated levels of educational support previously reported in the literature [18,30,31].

In contrast to valproate, the findings pertaining to the learning and memory functions of children exposed to carbamazepine, lamotrigine, and phenytoin in monotherapy are less clear. While children exposed to these three AEDs all demonstrated significantly lower adjusted mean scores on the Learning Index as compared with the children in the normal comparison group, this finding did not hold up consistently at the subtest level. Specifically, only children exposed to lamotrigine exhibited significantly decreased verbal learning efficiency on the Word Pairs subtest with a similar nonsignificant trend evident for carbamazepine. None of the three AED groups exhibited significantly decreased visual learning efficiency on the Dot Locations subtest, although children exposed to phenytoin trended in that direction. Finally, only children exposed to lamotrigine exhibited significantly lower adjusted mean scores on the Attention Concentration Index as compared with the children in the normal comparison group. However, this finding of poor auditory/verbal working memory did not hold up at the subtest level. Therefore, further research will be required to delineate the potential risks to learning and memory functions in children of mothers who were prescribed carbamazepine, lamotrigine, and phenytoin in monotherapy during their pregnancies.

The strengths of the NEAD study include its prospective design, blinded cognitive assessments using standardized measures, and detailed monitoring of multiple potential confounding factors. Study limitations include a relatively small sample size, loss of enrolled subjects to follow-up, lack of randomization, inadequate pharmacokinetics, and absence of an unexposed control group during pregnancy, which necessitated using a subset of children from the six-year-old standardization sample of the CMS for this report. Additionally, results are presented here for a large number of exploratory endpoints, and statistical analyses did not adjust for multiple comparisons. Results should be interpreted in the context of the number of analyses performed. As a result, future prospective studies should measure antiepileptic drug levels to better assess intrauterine exposure. Observational studies, such as the NEAD study, are vulnerable to confounding factors related to baseline characteristics, which make conclusions about causal effects more difficult. However, randomized pregnancy trials of fetal AED exposure in humans are not possible. Although our analysis suggests that baseline group differences do not explain our findings, additional research is needed to confirm these findings in larger prospective study samples that also include newer AEDs as well as a control group recruited from the same research sites.

In conclusion, most women with epilepsy cannot avoid the use of antiepileptic drugs during pregnancy because of the risk from seizures to both the mother and child. The findings from this report lend further support for our previous recommendation [17] that valproate is a poor first choice AED for most women of childbearing potential. However, a few women with generalized epilepsy can only have their epilepsy controlled by valproate. As a result, women with epilepsy should be made aware of the medical and neuropsychological risks and benefits of individual medications and dosages to themselves as well as potentially to their children during their childbearing years so that they can make informed decisions about their treatment.

Declaration of interest

Dr. Cohen reports that he is the author of the Children's Memory Scale; Dr. Meador has received research support from the National Institutes of Health, the Patient-Centered Outcomes Research Institute, UCB Pharma, and Sunovion Pharmaceuticals, and travel support from UCB Pharma. The Epilepsy Study Consortium pays Dr. Meador's university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals; Dr. May reports no disclosures; Ms. Loblein reports no disclosures; Dr. Conrad reports no disclosures; Dr. Baker was in receipt of educational grants from UCB and Sanofi Aventis and was an expert witness on Fetal Valproate Syndrome; Dr. Bromley reports that during the period overlapping the running of this project her institution received lecture fees from Sanofi-Aventis (2 occasions), she also received conference travel support from UCB Pharma (one occasion), and she provided expert testimony pertaining to fetal anticonvulsant syndrome; Dr. Clayton-Smith reports that she works with a group of professional offering medical advice to UK Fetal Antoconvulsant Syndrome Support Groups, but receives no benefits or remuneration for these services; Dr. Kalayjian reports that her husband owns Johnson & Johnson stock; Dr. Kanner, reports no disclosures; Dr. Liporace is on the Speaker's Bureau for UCB Pharma; Dr. Pennell has received research support from the National Institutes of Health and the Epilepsy Foundation, and honoraria and travel support from American Epilepsy Society, Epilepsy Foundation, National Institutes of Health, and academic institutions for CME lectures; Dr. Privitera reports grants and consulting fees from GW/Greenwich Pharma, grants and consulting fees from SK Life Science, consulting (DSMB) fees from Astellas, and grants from Epilepsy Foundation, NIH. He reports that none of this work is related to the submitted manuscript; Dr. Loring has received research support from the National Institutes of Health and Medtronic. Dr. Loring reports being a consultant for NeuroPace. He reports that his spouse is on the Speaker's Bureau for Biogen, Genzyme-Sanofi, Teva, and Novartis. Dr. Loring serves on the editorial boards for Epilepsia, Neuropsychology Review, and Archives of Clinical

Neuropsychology. He receives royalties from Oxford University Press, and 50% of his clinical effort involves neuropsychological testing, including Wada testing.

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Appendix A

NEAD Study Group: *Arizona Health Sciences Center, Tucson, Arizona*: David Labiner MD Jennifer Moon PhD, Scott Sherman MD; *Baylor Medical Center, Irving Texas*: Deborah T. Combs Cantrell MD, *University of Texas-Southwestern, Dallas Texas:* Cheryl Silver PhD; *Case Western Reserve University, Cleveland, Ohio*: Monisha Goyal MD, Mike R. Schoenberg PhD; *Columbia University, New York City, NY*: Alison Pack MD, Christina Palmese, Ph.D, Joyce Echo, Ph.D; *Emory University, Atlanta, Georgia*: Kimford J. Meador MD, David Loring PhD, Page Pennell MD, Daniel Drane PhD, Eugene Moore BS, Megan Denham MAEd, Charles Epstein MD, Jennifer Gess PhD, Sandra Helmers MD, Thomas Henry MD; *Georgetown University, Washington, DC*: Gholam Motamedi MD, Erin Flax BS; *Harvard – Brigham & Women's, Boston, Massachusetts*: Edward Bromfield MD, Katrina Boyer PhD, Barbara Dworetzky ScB, MD; *Harvard – Massachusetts General, Boston, Massachusetts*: Andrew Cole MD, Lucila Halperin BA, Sara Shavel-Jessop BA; *Henry Ford Hospital, Detroit, Michigan*: Gregory Barkley MD, Barbara Moir MS; *Medical College of Cornell University, New York City, New York*: Cynthia Harden MD, Tara Tamny-Young PhD; *Medical College of Georgia, Augusta, Georgia*: Gregory Lee PhD, Morris Cohen EdD; *Minnesota Epilepsy Group, St. Paul, Minnesota*: Patricia Penovich MD, Donna Minter EdD; *Ohio State University, Columbus, Ohio*: Layne Moore MD, Kathryn Murdock MA; *Riddle Health Care, Media, Pennsylvania*: Joyce Liporace MD, Kathryn Wilcox, BS; *Rush University Medical Center, Chicago, Illinois*: Andres Kanner MD, Michael N. Nelson PhD; *The Comprehensive Epilepsy Care Center for Children and Adults, St. Louis, Missouri*: William Rosenfeld MD, Michelle Meyer MEd; *St. Mary's Hospital, Manchester, England*: Jill Clayton-Smith MD, George Mawer MD, Usha Kini MD; *University Alabama, Birmingham, Alabama*: Roy Martin PhD; *University of Cincinnati, Cincinnati, Ohio*: Michael Privitera MD, Jennifer Bellman PsyD, David Ficker MD; *University of Kansas School of Medicine - Wichita, Wichita, Kansas:* Lyle Baade PhD, Kore Liow MD; *University of Liverpool, Liverpool, England*: Gus Baker PhD, Alison Booth ClinPsyD, Rebecca Bromley PhD, Claire Barrie BSc, Alison Gummery BSc, Rebekah Shallcross PhD; *University of Miami, Miami, Florida*: Eugene Ramsay MD, Patricia Arena PhD; *University of Southern California, Los Angeles, California*: Laura Kalayjian MD, Christianne Heck MD, Sonia Padilla PsyD; *University of Washington, Seattle, Washington*: John Miller MD, Gail Rosenbaum BA, Alan Wilensky MD; *University of Utah, Salt Lake City, Utah*: Tawnya Constantino MD, Julien Smith PhD; *Walton Centre for Neurology & Neurosurgery, Liverpool, England*: Naghme Adab, MD, Gisela Veling-Warnke MD; *Wake Forest University, Winston-Salem, North Carolina*: Maria Sam MD, Cormac O'Donovan MD, Cecile Naylor PhD, Shelli Nobles MS, Cesar Santos MD. **Executive Committee:** *Dartmouth Medical School, Hanover, New Hampshire*: Gregory L. Holmes MD; *Stanford University, Stanford, California*: Maurice Druzin MD, Martha Morrell MD, Lorene Nelson PhD; *Texas A & M University Health Science Center, Houston, Texas*: Richard Finnell PhD; *University of Oregon, Portland, Oregon*: Mark Yerby MD; *University of Toronto, Toronto, Ontario*: Khosrow Adeli PhD, Peter Wells Pharm.D. **Data and Statistical Center:** *EMMES Corporation, Rockville, Maryland*: Temperance Blalock AA, Nancy Browning PhD, Linda Hendrickson, Bernadette Jolles MA, Meghan Kelly Kunchai MPH, Hayley Loblein MA, Ryan May PhD, Yinka Ogunsola BS, Phyllis Zaia Renehan BS, Jamie Winestone BS, Mark Wolff PhD, Thad Zajdowicz MD, MPH.

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