Recent investigations of children with childhood absence epilepsy (CAE) have reliably demonstrated that CAE is not a syndrome free of cognitive or behavioral comorbidity. Particularly problematic is attentional impairment, not only because of attention's effects on cognitive and school performance but also due to its behavioral effects such as attention deficit hyperactivity syndrome (ADHD) (1). In the absence of clinical trials characterizing performance prior to treatment initiation, however, and evaluation of specific treatment risks from drugs or potential treatment benefit from EEG normalization, potential contributions to attention performance have not been independently characterized. Studies in adults have demonstrated that medications often used to treat CAE are also associated with differential risk of cognitive impairment (2). Further, potentially contributing to diminished attention are the effects of abnormal EEG discharges (3). Finally, the contributions of abnormal brain substrate giving rise to epilepsy versus AED treatment have been difficult to establish independent of the above factors (4). These issues are of considerable clinical and theoretical importance, not only to identify optimal CAE treatment associated with the least risk of cognitive side effects but ultimately to maximize school and vocational outcomes in these children.

Cognitive testing is increasingly used as an outcome measure in clinical trials to characterize this important feature of treatment tolerability. Cognitive testing, however, is less frequently employed to categorize individual subject performance to characterize various treatment risks. The Conners’ Continuous Performance Test (CPT), a classic approach assessing sustained attention in absence epilepsy beginning in the early 1960s (5), provides a measure that characterizes the likelihood that the individual’s performance reflects clinically relevant attention impairment (i.e., Confidence Interval, or CI). By operationalizing individual CPT performance using Confidence Interval data in children completing the multi-center CAE trial (6), Masur and his colleagues define the frequency of attention impairment seen in children with CAE before, or within 1 week, of starting AED therapy. Using this clinically relevant criterion, over one-third of the 408 children (36%) demonstrated impaired attention function at study entry.
Because CPT testing was conducted either before or within 1 week of starting AED, the attentional impairment is not related to medication side effects (there were no differences between performance of children tested before starting AED and those tested within 1 week of starting treatment) and reflects either primary or secondary disease effects.

Differential AED attentional effects have already been established by the CAE trial (6) and, in fact, ethosuximide was recommended over valproate as the initial CAE treatment choice, despite equivalent efficacy, because valproate was associated with greater CPT attentional impairment. Glauser and colleagues (6) did not characterize individual performance, however, and when identifying those with a clinically relevant attention impairment or not, nearly one half of CAE children taking valproate (49%) had impaired attention at study completion, significantly higher than either ethosuximide (32%) or lamotrigine (24%). Individual frequency characterization also allows relative treatment risks to be calculated, and although not included in their analyses, ethosuximide is associated with a 17% absolute risk reduction (95% Confidence Interval = 6%-28%) of impaired attention compared to valproate, the two comparably effective CAE treatments (Relative Risk Reduction = 35%, 95% CI = 13%-57%; Number Needed to Treat = 6, 95% CI = 4–16). Thus, for every 6 children with CAE treated with ethosuximide rather than valproate, impaired attention in one child is avoided.

Are the negative effects of AED treatment offset at all by successful CAE treatment? Negative cognitive effects of abnormal EEG discharges are a common clinical concern (3, 7, 8) and successful normalization of the EEG provides an opportunity to mitigate CAE’s attentional impairment. Unfortunately, eliminating spike-wave bursts of at least 3-seconds duration had no beneficial effect on attention in this population, suggesting that attentional impairment of CAE can be considered an “essential comorbidity” (9) and not easily modifiable with standard AED interventions. This provides another confirmatory piece of information to the steadily emerging literature in pediatric epilepsy that cognitive comorbidities are common at the time of initial epilepsy diagnosis (10) and do not simply reflect seizure expression or epilepsy duration. Rate of epileptiform activity associated with slower processing speed has been previously described (11), although the present data derived from a longitudinal intervention approach do not support this. This is a disappointing finding: if attentional impairment were secondary to EEG discharges, then impaired attention would be partially remediated following successful treatment of EEG discharges.

A novel aspect of this report is the statistical modeling of the neurocognitive contributions to achievement test performance. Although school achievement is multidetermined and multifactorial, the relationship of attention to other cognitive processes has been poorly defined. Even this context in which normal cognitive performance is observed despite poor attention, greater understanding of the contributions of different cognitive operations can be obtained. This study, however, was designed to evaluate treatment effectiveness in CAE and did not include a control group. Thus, CAE children may demonstrate relative impairments in cognition even when scores are in the “normal” range based upon standardization sample characteristics.

Masur and colleagues observed the expected correlations across measures of attention, memory, executive function, and academic achievement scores used in the CAE study but also established a direct, sequential effect across these cognitive constructs using the sophisticated structural equation modeling technique of path analysis. Attention exerted a direct effect on memory. Memory, in turn, had direct influence on executive function, which subsequently exerted a direct effect on achievement test scores. Thus, while attention did not directly affect academic achievement, attention has secondary influences on achievement scores by having direct effects on memory and secondary effects on executive function. While memory also did not exert a direct effect on achievement, memory influenced achievement through its effects on executive function.

This sequential model of cognitive processes confirms the direct and indirect influences of lower level attention constructs on higher level constructs. That poor attention has significant upstream effects is of little surprise to clinical epilepsy researchers. However, the direction and influences have not been precisely characterized. This relationship was derived from achievement scores that were in the normal range with relatively little performance variability, decreasing the likelihood of statistical significance. This suggests relatively robust statistical relationships across these constructs and may even be greater in children with greater cognitive burden (1).

Attention is a lower level building block on which higher order cognitive abilities develop and is related to achievement through both direct and indirect connections. The influence of memory and executive function can provide a window of opportunity in which intervention strategies targeted at maximizing memory and executive function can maintain normal achievement scores in this population, even in the absence of meaningful benefit following normalization of the EEG. As greater attention is given to minimizing the cognitive comorbidities associated with epilepsy and epilepsy treatments—reflecting concerns of the treating physician, the patient, and the patient’s family—various interventions designed to maintain existing function and minimize decline will provide significant quality of life benefit.

by David W. Loring, Ph.D.

References


Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Section #1  Identifying Information

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2.  First Name    David    Last Name Loring    Degree Ph.D

3.  Are you the Main Assigned Author?  □ Yes  □ No

   If no, enter your name as co-author:

4.  Manuscript/Article Title:

5.  Journal Issue you are submitting for:

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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<th>Type</th>
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<th>Money to Your Institution*</th>
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*  This means money that your institution received for your efforts on this study.
**  Use this section to provide any needed explanation.
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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Thank you for your assistance.

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