Commentary
The study by Dlugos et al. adds to the important information on impaired attention, measured with the Continuous Performance task (CPT), in childhood absence epilepsy (CAE) that has emanated from the large multisite treatment study CAE by Glauser and colleagues (1–3). About 36% of CAE have impaired attention with errors of omission rather than of commission before treatment that improve in 26% of those randomized to valproate, 43% of those randomized to ethosuximide, and 47% of the lamotrigine treated patients (3). The attentional impairment, however, worsened in the valproate cohort overall. These findings are evident 16 to 20 weeks (3) and 12 months (1) after beginning treatment.

Dlugos et al.’s EEG study has shown that duration of seizures is differentially associated with the attentional impairment and treatment effect. Those children who experienced seizures lasting 20 seconds or more had significantly more errors of omission 16 to 20 weeks after starting treatment with one of the three previously mentioned antiepileptic drugs (AEDs). However, in terms of the treatment effect, freedom from failure and seizure freedom were significantly related to longer duration of the shortest seizure and longer median duration of all seizures irrespective of treatment arm.

What do these findings mean in terms of advancing our understanding of the nature of the attentional impairment in CAE? This question is particularly relevant because the baseline CPT in Dlugos et al.’s study was not administered while the children were having an EEG recording. The CPT findings, therefore, reflect some combination of ictal and interictal attentional impairments, as originally proposed by Mirsky et al. (4). But recent fMRI/EEG studies in CAE with and without CPT and fMRI studies during CPT shed some light on what is distracting these children.

An fMRI/EEG study of 22 children with CAE whose AEDs were withheld during the 48 hours prior to the study demonstrated increased activation of the thalamus, frontal, primary visual, auditory, sensory, and motor cortex but deactivation in lateral and medial parietal, cingulate, and basal ganglia during both ictal and interictal spike wave discharges (5). Furthermore, errors of omission on the CPT that occurred during a seizure were associated with increased and decreased activation in these same thalamocortical regions. Most interestingly, not all seizures involved impaired performance on the CPT.
and abnormal thalamocortical activity. In fact, normal CPT performance occurred during the seizures with the shortest duration. Similar to Dlugos et al.'s EEG findings, short duration of seizures appears to not be associated with attentional impairment in CAE. Increased connectivity in the thalamus and extensive decrease in connectivity in the default-mode network, dorsal attention network, central executive network, and salience network also occurred during spike wave discharges in the 16 CAE youth studied by Zhang et al. (6).

But not all absence seizures involve impaired attention and prevalent attention deficit hyperactivity disorder (ADHD); the inattentive type in CAE is not associated with seizure frequency and control (7). Furthermore, the findings of the CAE multisite study suggest that despite freedom from failure and decrease in seizure frequency, 49% of the children on valproate, 32% of those on ethosuximide, and 26% on lamotrigine continued to have deficits in attention 16 to 20 weeks and 12 months after beginning treatment (1, 3). Together, these findings emphasize that these children also have interictal poor attention irrespective of seizure control.

Similar high rates of the inattentive type of ADHD (see review in [8]) in children with localization related epilepsy and in pediatric CNS disorders, such as traumatic brain injury (see review in [9]) suggest that the interictal impaired attention of CAE might be a nonspecific symptom of widespread CNS involvement of the attentional network. Identification of the interictal mechanisms of the deficits in attention—as well as the shared and distinct features of the ictal attentional impairment in children with different epilepsy syndromes—is needed to delineate the underlying mechanisms. A multisite fMRI, EEG, and CPT study on a large sample of children with these different epilepsy syndromes is needed to begin to bridge this important gap in our knowledge.

The poor treatment response of the deficits in attention in the multisite CAE study is an additional reminder, as repeatedly shown over the past two decades, that CAE is not a benign disorder. Impaired attention can hinder children's academic performance, communication, and social relationships, areas of functioning that are impaired in children with epilepsy (see review in [8]) and impact the long-term outcome (10) and quality of life of these children (11). The findings of the CAE multisite study clearly highlight the need to screen every child with CAE for an attentional impairment and the unmet and untreated need of these children. They also underscore the need for focused intervention for this comorbidity. Although there appears to be a treatment effect of stimulants in children with epilepsy and ADHD, the possibility of increased seizure frequency needs to be ruled out in both children with good and poor seizure control [8]. Impaired attention in CAE and other pediatric epilepsy syndromes at onset of these disorders (see review in [8]) and prior to treatment further emphasize the theoretical and clinical importance of pursuing both basic science and treatment studies to address this important comorbidity and its treatment.

Finally, the lack of an association between the EEG findings and measures of executive function in Dlugos et al.'s study might appear surprising given the predominant involvement of the frontal lobe in CAE. However, the lag in maturation of executive functions in children is attributed to the late occurring frontal lobe morphometric changes involving volume and thickness during late childhood and adolescence (12). The young age range of the children in Dlugos et al., 2.5 to 13 years, probably underlies this finding.

by Rochelle Caplan, MD

References


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.

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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:  Epilepsy Currents

Section #2 The Work Under Consideration for Publication
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<th>Money to Your Institution*</th>
<th>Name of Entity</th>
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* This means money that your institution received for your efforts on this study.
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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.
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