Absence epilepsy: Characteristics, pathophysiology, attention impairments, and the related risk of accidents. A narrative review

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ARTICLE INFO

Abstract

Objective: Absence epilepsy (AE) is related to both cognitive and physical impairments. In this narrative review, we critically discuss the pathophysiology of AE and the impairment of attention in children and adolescents with AE. In particular, we contextualize the attentive dysfunctions of AE with the associated risks, such as accidental injuries.

Data source: An extensive literature search on attention deficits and the rate of accidental injuries in AE was run. The search was conducted on Scopus, Pubmed, and the online libraries of the University of Twente and Maastricht University. Relevant references of the included articles were added. Retrospective and prospective studies, case reports, meta-analysis, and narrative reviews were included. Only studies written in English were considered. Date of last search is February 2020. The keywords used were “absence epilepsy” AND “attention”/ “awareness”, “absence epilepsy” AND “accidental injuries”/”accident”/”injuries”.

Results: Ten retrospective and two prospective studies on cognition and AE were fully screened. Seventeen papers explicitly referring to attention in AE were reviewed. Just one paper was found to specifically focus on accidental injuries and AE, while twelve studies generally referring to epilepsy syndromes – among which AE – and related accidents were included.

Conclusion: Absence epilepsy and attention deficits show some patterns of pathophysiological association. This relation may account for dysfunctions in everyday activities in the pediatric population. Particular metrics, such as the risk related to biking in children with AE, should be used in future studies to address the problem in a novel way and to impact clinical indications.

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1. Introduction

Around 60 million people worldwide have epilepsy, making it one of the most prevalent neurological disorder. In high-income countries, about 50 per 100,000 children are diagnosed with epilepsy every year, accounting for 25% of new epilepsy cases [1]. Epilepsy refers to a brain condition characterized by enduring predisposition to generate seizures [2], of which more than 40 types have been cataloged in the latest classification of the International League Against Epilepsy (ILAE) [3]. Clinical signs and symptoms of seizures are varied, ranging from changes in perception to elementary motor manifestations or loss of consciousness [3].

Here, we focus on absence epilepsy (AE), a particular type of genetic generalized epilepsies (GGEs) characterized by relatively brief (3–30 s) periods of inattention and 3 Hz spike–wave discharges (SWD) as a characteristic seizure signature [4–6].

While initially considered a benign syndrome, AE is now associated with mild motor signs during seizures and with cognitive impairments both in the ictal and interictal period [5,6]. For instance, children with
childhood absence epilepsy (CAE) usually show lower results in attentional tests than typically developed peers [7–9]. This may account for subsequent impairment on everyday activities, such as scholastic performances [10]. Furthermore, attentive deficits and occasional failures in their motor system may be related to the more frequent occurrence of accidental injuries. Indeed, a higher risk of accidents in AE has been reported [11–20].

In this review, we discuss the pathophysiology involved in the impairment of attention in children and adolescents with AE. We consider the risks associated with attentive dysfunctions, such as accidental injuries. Finally, we argue that focusing on realistic, measurable, and specific variables, such as the risk related to biking for children with AE, may give new insights both for further research and clinical practice.

The literature search conducted to realize this review comprises retrospective and prospective studies, case reports, meta-analysis, and narrative reviews. Scopus, PubMed, and the online libraries of the University of Twente and Maastricht University were used as search engines, together with relevant references of included articles. Only papers in English were considered. Last search was run in February 2020. Key words used were the following: “absence epilepsy” AND “attention”/“awareness”, “absence epilepsy” AND “accidental injuries”/“accident”/“injuries”. From this search, ten retrospective and two prospective studies on cognition and AE were fully screened. Seventeen papers explicitly referring to attention in AE were reviewed. Just one paper was found to specifically focus on accidental injuries and AE, while twelve studies generally referring to epilepsy disorders – among which AE – and related accidents were included.

2. On the definition of absence epilepsy and its characteristics

Commonly, an individual is considered absent if this person is not present either physically or mentally. The term “absence” denotes that something is not there, a general or precise perceivable lack. If we specifically refer to the clinical environment, the word “absence” represents a peculiar kind of ictal activity in patients with GGE, comprising a characteristic symptomatology and epidemiology. In the clinical domain, this designation maintains hints of its original meaning. Several questions arise as a consequence: what is “not present” during an absence seizure? What are the people diagnosed with AE missing?

The expression “absence epilepsy” is relatively recent. This condition was used to be referred to as “petit mal” [4]. Part of the distress linked to AE is caused by a transient “switch-off” between 3 and 30 s long, a momentary lack of awareness and responsiveness to the external world. The electroencephalography (EEG) of patients with AE most often shows specific patterns during absences, i.e., transient and abrupt bursts of large amplitude generalized spike–wave complexes between 3 Hz and 4.5 Hz [21], with a frontal predominance in both human and rodent models [22]. The length of the ictal activity is ≥3 s, with an average duration of 9.4 s ± 7 s [22]. During these brief lapses, it is challenging to extrapolate information about what the patients are experiencing. While from the outside, behavioral symptoms are recognizable (e.g., staring, unresponsiveness, eye fluttering, muscle jerks, face automatisms, or behavioral arrest [5,22]), from an internal point of view, the scenario is not clear at all. Some patients report complex or simple hallucinations during absence seizures, both of visual and auditory nature [23].

2.1. Different types of absences

Although the characteristics of AE are mainly similar across patients, distinct, specific syndromes exist. The two most prominent ones are CAE and juvenile absence epilepsy (JAE). These two disorders differ mainly in the age range of occurrence in the patients: the average first peak onset of CAE is at 6–7 years, whereas for JAE, it is around 12 years [5]. Childhood absence epilepsy is considered the most common pediatric epilepsy syndrome, with 10–17% of children with epilepsy being diagnosed as CAE [24]. Females are more affected than males. Childhood absence epilepsy is characterized by frequent seizures (a few to hundreds per day, with a great variability among patients [2]) and by bilateral synchronous and symmetrical SWD on the EEG at 3 Hz, on an otherwise normal background pattern [25]. On average, children with CAE are responsive to treatments, with a complete remission rate in around two-third of patients [26,27]. Conversely, JAE shows a lighter impairment of awareness, albeit a longer duration of absences. For patients with JAE, generalized tonic–clonic seizures also commonly occur and have been reported in almost 80% of cases [28]. Typically, around half of patients with JAE does not reach a complete freedom from seizures, especially when the absences appear together with other comorbidities (e.g., attention-deficit/hyperactivity disorder (ADHD), psychiatric disorders, neurological dysfunctions) or types of seizures [4]. The likelihood of JAE symptoms to persist until adulthood is higher than for patients with CAE [5]; other kinds of seizures are usually present as well [25].

Different types of absence seizures have been classified, mostly divided into two categories: typical and atypical absence. Typical absences in the EEG appear as 3 Hz generalized spike–wave complexes, between 3 and 30 s long. In addition to the standard clinical aspects, special features can be present, such as myoclonic absence seizures and eyelid myoclonia with absence [6,25]. Typical absences can be found in a series of generalized epileptic syndromes other than AEs, such as juvenile myoclonic epilepsy (JME) and Jeavon’s syndrome [25]. On the other hand, atypical absences in the EEG manifest a less abrupt onset and offset, longer duration, and slower SWD (1.5–2.5 Hz) with lower amplitude [29]. Usually atypical absences show a slower EEG background and are associated with a poorer outcome, multiple other seizure types, and resistance to treatment [25,29]. Atypical seizures can be found in Lennox–Gastaut syndrome [25].

2.2. Does absence mean unconsciousness?

Many clinical and scientific proofs argue that consciousness – or at least aspects related to it – is the most prominent impaired domain of AE [6,22]. Blumenfeld and Meador discuss the importance of consciousness to describe epileptic seizures [30]. On this matter, a new classification of seizure types was released [3] in 2017 by the ILAE, which includes the impairment of consciousness as a distinction criterion for epilepsy [30,31]. Awareness and its impairment (i.e., a surrogate marker of consciousness) has been introduced as a fundamental feature to classify focal onset seizures [3]. Together with awareness, memory, responsiveness, and sense of self are considered elements of consciousness. These aspects are useful to categorize generalized seizures as well, although not included in the ILAE classification. Indeed, during absences, most of these components are impaired: unresponsiveness to high-order tasks, no memories of the events during the seizure, and unawareness of ongoing activities are the usual features of AE [4–6,32]. Simple, automatic behaviors, such as finger tapping or eating, are generally preserved [33].

It is debatable if the unresponsiveness of patients with AE is a consequence of a lack of focus and attention orientation, or if it is a problem occurring earlier in the sensorimotor domain. Most of the time, these symptoms seem to be unrelated to any impediment of the arousal system [6]. Patients with AE are alert and completely awake during seizures, even though their reaction time (RT) is longer and cognitive functions often show some decline [4,33,34]. Lüders and colleagues [35] have presented a classification of loss of consciousness types in different epileptic syndromes, stressing the idea that a great variety of alteration in consciousness is present throughout or in proximity to ictal events. They define loss of consciousness as the concomitant existence of unresponsiveness and memory loss. Both these elements are objectively measurable during acute absences.

This overall problem in the definition of what consciousness and absence really are has some traits of epistemological nature [36]. Indeed,
to advance the understanding of AE, it is important to use standardized definitions. This is why it may be preferred to focus on peculiar descriptive elements related to the symptomatology of AE.

2.3. The neural substrate of absence seizures

Traditional theories regarding the pathophysiology of AE are mainly two: the centrencephalic theory and the generalized corticoreticular theory [25]. Both of them recognize a primary role of the reticular system in the mechanisms producing absence seizures [6,25], with different significance given to the functions of the neocortex. The centrencephalic theory considers the thalamus as the primary driver for the beginning of ictal activities: absences would originate in the central integrating system of the higher brainstem (i.e., centrencephalon) [4], and just afterwards, they would reach the cortex. The corticoreticular theory argues, instead, that the projections of the reticular system to the cortex are essential for the generation of SWD right from the beginning [37]. Indeed, the corticoreticular theory indicates that absences result from hyperexcitability of the cortex and its interaction with ascending stimuli from the thalamus. A third, more recent, theory about AE and its underlying brain mechanisms is the cortical focus theory [38]. It is prevalently based on contemporary results from animal models, and it assumes the presence of a cortical focus of absence seizures. Subsequent oscillations in the thalamocortical network develop into the generalization of the epileptiform activity [25]. According to this theoretical proposal, no specific driver is needed for absences to occur [6,25,26].

The centrality of the corticothalamic pathway in the generation of absence seizures is further substantiated with functional magnetic resonance imaging (fMRI) and EEG studies, reporting activation patterns in the thalamus and cortical areas such as the frontal and parietal cortices in patients with AE [6,8,25,39]. Magnetoencephalography (MEG) studies show focal cortical activity during and preceding SWD in AE [5,6]. These focal abnormalities are especially seen in the regions belonging to the default mode network (DMN) in JAE, while fMRI outcomes show deactivation patterns in the DMN and in other cortical areas [6]. A decrement in blood–oxygen-level dependent (BOLD) activation was also seen in the medial prefrontal cortex and temporal poles [25].

In summary, the core network of absence seizures and their manifestations lies in the thalamus, the DMN, the striatum and other subcortical areas such as the reticular structures of the pons, and the cerebellum [25]. In view of this evidence, absences may be described as generalized seizures, presumably with a focal or regional onset.

2.4. Cognition in absence epilepsy

The cerebral changes at the base of AE also impact cognition. Literature on AE and cognitive abilities is principally comprised of retrospective reports and of few prospective studies investigating the effects of antiepileptic drug (AEDs) therapies on cognitive performances. Ninety-one patients with AE were tested on verbal and spatial short-term memory tasks [40]. As a result, transitory cognitive impairment (TCI) was evident in half of the sample. In this study, the synchronicity between SWDs and the presentation of the target stimulus to be recalled was shown to be associated with a mnemonic impairment. In addition, the level of difficulty of the task was positively related to the cognitive outcomes: the more complex the trial was, the greater the TCI appeared. Here, a threshold of 5 s was calculated for clinical symptoms to be manifested in AE. Another study [41] considers the clinical manifestation to start earlier, 1.5 s after the beginning of the SWDs.Indeed, the evidence from both humans and animal models exhibits that TCI is present in epilepsy even without manifest seizures. The anomalous interictal epileptiform activity may momentarily disrupt cortical processing as well [32,42]. A follow-up retrospective survey [43] assessed the main cognitive fields (i.e., intelligence, attention visual–perceptual function, language, memory, and learning) in 31 children with CAE or JAE, based on Baron’s distinction of neurocognitive domains in children [44]. In this study, educational achievements were also included, collected with reports and academic evaluations filled by school-specialists. Other than on group variations, they also focused on the individual changings of cognitive development. In a follow-up period of 1.7 ± 0.95 years, an actual improvement in sustained attention was registered, which was lower than average during the first assessment. On the other hand, receptive vocabulary showed a decrease overtime, even though its level was not different from the normative mean. Group scores were lower than average for intelligence quotient (IQ), visual motor integration, perceptual organization, processing speed, and KT. Mild-to-severe difficulties at school have been recorded in the majority of the children, while 38% of the sample manifested learning problems. Except from sustained attention, most of these cognitive domains remained impaired overtime, even after the termination of seizures.

Although the impairment of cognition and its everyday consequences (e.g., school performance) is a well-recognized fact in AE, just two prospective studies have been investigating this relation [10,45]. In these papers, children diagnosed with either CAE or JAE were followed respectively for 10 and 12 months. The main goal of both papers was to assess the effects of the introduction of AEDs on cognition. In one of the studies [10], the pharmacological treatment has been shown to improve specific cognitive outcomes in children with AE, especially visual memory, fine-motor fluency, and attention. Interestingly, an improvement in attention and fine-motor functions after 10 months was seen in the control group as well, arousing suspect that the enhancement may in part be related to a practice effect. The other prospective research [45] registered attentional deficit both at the beginning of the study and after the 12-month follow-up, even though the attentional deficits improved and the pharmacological treatment was successful in reducing or eliminating seizures.

Motor activity is impaired in AE as well, and this may cause additional deficits in high-order cognition. Bilateral myoclonic jerks, atonic rhythmic nodding, complex automatism, circling, ictal head version, horizontal nystagmus, and unilateral repetitive myoclonus are the principal impairments in motion that AE can provoke [6]. A study done on 416 participants [41] found pause in activity and staring as the most common motor features of AE, even though they rarely occur alone. Unfortunately, proofs of a direct relation of motor symptoms and SWD in AE are lacking. The evidence of their correlation lies in some peculiar observations: the timing usually coincides between motor dysfunctions and epileptiform events; also, the neural correlates of the motor impairment relate to the brain locations involved in absences [6].

The higher incidence cognitive impairment has on school performance and everyday activities is often translated into social complications for children with AE: isolation and general lower level of employment are just some of them [8]. An effective assessment of the relations between AE and cognition can be really useful to guarantee the general wellbeing of the patients. In this regard, it is essential to converge into the assessment of definite cognitive abilities, which can give new proofs of a direct link between the illness and its cognitive symptoms and motivate the development of connected interventions. Attention, for example, is one of the cognitive aspects influenced the most by absence seizures. Because of its multifactorial nature and its fundamental role for many other cognitive aspects, it is meaningful to consider it closely.

3. On attention and its definition

The term “attention” implies a set of different mechanisms, both voluntary and automatic. These features can be summarized into specific subtypes of attention, extensively investigated in cognitive psychology: sustained attention, selective attention, generalized attention, alternate attention, spatial attention, and working memory (WM) as well. Attention is considered a building block for many cognitive and motor
functions, and it is, therefore, one of the most widely investigated cognitive domain. Besides the classical theories [46–50], novel models of attention have been postulated. The latest neuropsychological and neuroscientific evidence depicts attention as part of multidimensional models composed by different substructures [51,52]. One of the most accredited theories partitions attention into three independent networks [53]: the alerting network, the orienting network, and the executive network. The first network activates and maintains vigilance, while the orienting network selects focal information from stimuli. On the other hand, executive control monitors possible conflicts between competing information. An alternative perspective, the multicomponent model of attention [51], claims that attention is founded by two constitutive aspects: the selectivity of attention (i.e., selective attention, impulsivity, focused attention, divided attention) and the intensity of attention (i.e., arousal and vigilance). Similarly, the two-network attention theory [8,54,55] considers the dorsal and the ventral networks as two distinctive attentive aspects. The dorsal network involves the orienting of attention and, therefore, goal-directed behaviors; the ventral network is involved in the reorientation of attention during the appearance of sudden stimuli.

Even though the theories on attention are numerous and reveal different details, they share some main characteristics, such as the multidimensionality of attention and the importance of neurophysiological and neuropsychological cues to assess attention. In this scenario, it is relevant to address the main physical counterparts of attention.

3.1. The neural substrates of attention

Over the last decades, the models of attention have been extensively investigated through neuroscientific studies. For instance, the three networks model [53,56] is based on evidence from neuropsychology and from neuroimaging techniques (i.e., positron emission tomography (PET)). Principally, every network has been associated with a neurophysiological counterpart: the alerting network with the brain stem arousal system and with the right-sided systems involved in sustained vigilance; the orienting network with the parietal cortex and the executive network with the midline frontal cortex and the anterior cingulate.

Correspondingly, neurophysiological evidence of the two-network attention theory [54] suggests that two partially segregated systems in the brain guide attention: the dorsal and the ventral networks. The dorsal network comprises the frontal eye field (FEF) and the intraparietal sulcus (IPS) (Fig. 1A). These regions are involved in the top–down selection of sensory information and in the response to goal-directed stimuli, implying a voluntary allocation of attention. On the contrary, the ventral network is lateralized in the right hemisphere and includes the ventral frontal cortex (VFC) and the temporoparietal junction (TPJ) (Fig. 1A), probably depending on the noradrenergic modulation of the locus coerulescens as well. The ventral network detects unexpected or unattended sensory events and the joint shifting of attention. In sum, the dorsal system filters the signals coming from the ventral system, while stimulus-driven signals deriving from the ventral system inhibit the dorsal system, allowing a refocus on salient stimuli [8,54,55]. It must be acknowledged that this model is mainly based on the visuospatial attentional system, even though dorsal and ventral networks are potentially supramodal systems [57,58]. Moreover, specific subcortical areas are relevant for attention too (Fig. 1B): the superior colliculus in the midbrain is involved in the elaboration of visual information and in gaze orientation, the pulvinar nuclei are engaged in visual elaboration and orientation, in particular, they act as a filter to external inputs [59].

The image of a dual system involved in the engagement of attention is widely accepted nowadays, although the functional organization and lateralization of the two networks and their interaction are still controversial points [58]. The two systems are specialized, but a dynamic interactive pattern between them must be established for a standard functioning of attention. In their recent review, Vossel and colleagues [58] summarize contemporary findings on the interaction of the two networks, providing evidence for the significant role of frontal areas, such as the inferior and middle frontal gyrus.

The models reported share some basic aspects but are not entirely comparable [60]. In this context, it is informative to examine attention in the domain of AE. In this way, we can identify the common mechanisms, which can help with the characterization of both AE and attention.

4. Absence epilepsy and attention

Epilepsy in general, and AE in particular, can be described as one of the factors that unconventionally modify attention [61]. It is not clear whether this impairment is just confined to the level of signal processing, or it derives from higher-order processing such as decision-making, motor impairment, memory degrading, or any combination of these aspects [33]. Several studies have assessed attentional dysfunctions in AE. Some of them focus on the direct influence of abrupt SWDs typical of absence [22,62], which manifest with a transient unresponsiveness and deficiency of attention. The majority of them [7–9,63–71] assesses the continuous cognitive deficits detectable both during ictal and normal activity. These papers present several types of prolonged attention impairments, which are explained either as a worsening in attentional performances on psychometric tests or as attention failure in everyday activities, such as school performance or accidental injuries. In this paragraph, we revise some of these studies.

Already in 1965, Mirsky and van Buren stated that absence seizures produce an impairment during the processing of external stimuli, rather than an actual transient loss of consciousness [32]. Afterwards, various studies on event-related potentials (ERPs) have been conducted to assess the centrality of signal processing in AE, with contrasting outcomes [4]. High variability in responsiveness has been reported both across patients and across conditions within the same patient [22]. From the first results, visual-evoked potentials appeared smaller in patients with AE [63]. In a recent study [64], interictal ERPs after the presentation of visual and auditory stimuli during a continuous performance task (CPT) showed a significantly smaller P3 component compared with controls. In the same study, they replicated their design on patients with focal impaired awareness seizures and found that both the latter group and CAE had smaller P300 for visual stimuli. On the contrary, for auditory stimuli, a smaller P3 was found just in the absence group. This evidence supports the existing differences between the auditory and the visual attentional systems [64]. The former seems to be more sensitive to absence seizures, probably due to shared physiological counterparts in the brainstem with AE.

Other EEG patterns are essential in defining attention impairment in AE. It has been speculated that the specific pattern of activation seen in the frontal areas of patients with AE may account for the cognitive deficits typical of this condition [7,65]. In most cases, longer seizure duration has been correlated with a more severe impairment in simple RT, CPT, scores and memory tests [5]. Moreover, higher amplitude and generalization of the ictal activity have been related to impairment in RT and other tasks [22]. A relation was also found between severe impairment in vigilance and memory and EEG features such as spike–wave duration, amplitude, rhythmicity, and frontocentral distribution [33]. It is argued that these results derive from disruption in patients’ information processing located in focal bilateral association cortex [33].

Further neuroimaging studies conducted with fMRI and EEG tried to define possible structural and functional elements associated with attentional dysfunctions in AE. Various outcomes [39,65,72] revealed disruption in dorsolateral prefrontal cortex (DPPC), orbitofrontal cortex (OFC), anterior cingulate, thalamocortical circuits, and motor/premotor basal ganglia, the same areas that play a crucial role in high-level cognitive activities. Killory et al. [8] were the first who specifically investigated the brain networks involved in attention disruption in CAE during interictal activity. Using fMRI, they measured the brain activity...
of patients with CAE during a CPT for sustained attention. Results showed significantly impaired functioning of attentional circuits like the anterior insula, the frontal operculum, and the medial frontal cortex, compared with healthy controls. Childhood absence epilepsy performed significantly worse in CPT compared with healthy subjects. Furthermore, the degree of impairment in the behavioral tests correlated negatively with fMRI activation of the medial frontal cortex during task.

Neuroimaging evidence is fundamental to define the actual degree of degradation of attention and other cognitive skills in patients with epilepsy. In this regard, the use of behavioral assessments is also valuable and especially important in clinical investigations.

4.1. The behavioral assessment of attention in AE

Several tests for the assessment of attentional subdomains are available for both patients with AE and healthy subjects. They objectively quantify attention in a comparable way, sharing a common performance metric: RT. Since the forties, the difference in RT has been considered a fundamental manifest variable to make inferences on the latent construct of attention [73]. In addition, errors (both of commission and of omission) represent a further objective variable often used to factually define attentional levels. Here, we will report the results of most of the attentional tests used in the pediatric population with GGE, summarized in Table 1.

Through the test of attentional performance (TAP) battery, Cerminara et al. [7] indicated an impairment of normal developmental processes of attentive networks segregation and integration in CAE [8]. Based on the two-network theory of attention [54,55], they assessed the selectivity and the intensity of attention levels in 24 children with CAE and in 24 healthy controls. They saw a notable impairment in alertness, divided attention, impulsivity, and selective attention. Interestingly, they claim that the higher variability found in RT in the group with CAE may account for a greater impulsivity and a deficient self-regulation, corroborating previous findings of control problems in this population. D’Agati and colleagues [65] evaluated executive function (EF) and attention of a group with CAE under treatment with valproic acid, presenting controlled seizures and negative EEG. They used classical cognitive tests for different domains. Attention was assessed via trail making test (TMT)-A and B. The most significant differences between the CAE and the healthy controls were found in planning, phonological
Table 1
Overview of tests to assess attention in children with AE and GGE.

<table>
<thead>
<tr>
<th>Tests of attention</th>
<th>Attention subtypes</th>
<th>Objective quantification</th>
<th>Num of sample</th>
<th>Results in pediatric GGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Attention Network Test (ANT)</td>
<td>Alerting, orienting, executive control</td>
<td>Changes in reaction time</td>
<td>Children with GGE: n = 37; controls: n = 37 [66]</td>
<td>Slower RT (overall mean RT (ms) = 814.7 ± 185.3 vs 702.8 ± 215.8, p = .019); Deficient executive control (RT (ms) = 166.9 ± 111.1 vs 115.9 ± 79.0, p = .026) [66].</td>
</tr>
<tr>
<td>Advanced Test of Attention (ATA)</td>
<td>Attention, response inhibition</td>
<td>Omission errors, commission errors, response time, response time variability</td>
<td>CAE group: n = 20, of which n = 12 without ADHD and n = 8 with ADHD; children with ADHD only: n = 20; controls: n = 20 [9]</td>
<td>12 CAE group without ADHD — impairment in selective attention: more omission errors in visual ATA (2.89(5.38) vs −0.16(0.77), p &lt; .001), higher RT in auditory ATA than healthy controls (0.29 (0.85) vs −0.21(0.9), p = .002), decreased RT variability than ADHD group (−0.37(0.77) vs 1.71(1.72), p = .001); CAE and comorbid ADHD — impairment in sustained attention: higher commission errors rate (4.68(4.44) vs 2.89 (5.38), p &lt; .001) and greater RT variability in visual ATA (0.39(1.20) vs −0.37(0.77), p &lt; .001), increased commission errors in auditory ATA than CAE group without ADHD (2.73(2.37) vs 0.40 (1.53), p &lt; .002) [9].</td>
</tr>
<tr>
<td>Continuous Performance Task (CPT)</td>
<td>Sustained attention, selective attention</td>
<td>Omission errors, commission errors, response time, correct detection</td>
<td>CAE group: n = 26; controls: n = 22 [8]</td>
<td>AE group: n = 9; focal impaired awareness seizures: n = 13; controls: n = 10 [64]</td>
</tr>
<tr>
<td>Trail Making Test (TMT-A,B)</td>
<td>Processing speed, sustained attention (TMT-A), divided attention, attention shifting (TMT-B)</td>
<td>Completion time (visual search task)</td>
<td>CAE group n = 15; controls = 15 [65]</td>
<td>Genetic epilepsy: n = 28; cryptogenic epilepsy: n = 26; controls: n = 48 [74]</td>
</tr>
<tr>
<td>Test of Attentional Performance (TAP)</td>
<td>Selective attention, divided attention, focused attention, impulsivity, arousal, vigilance, working memory, etc.</td>
<td>Omission errors, commission errors, response time</td>
<td>CAE group: n = 24; controls: n = 24 [7]</td>
<td>Higher RT: TMTA total time = 44.5 ± 13.5 vs 31.9 ± 8.7, p = .007, MTMB total time = 146.1 ± 50.5 vs 106.4 ± 10.3, p = .041. Worse results in sustained and divided attention [65].</td>
</tr>
<tr>
<td>Choice Reaction Time (CRT) tests</td>
<td>Alertness, motor speed</td>
<td>Correct/Incorrect responses, commission errors, omission errors, latency</td>
<td>Group with epilepsy: n = 112; controls: n = 112 [68]</td>
<td>Higher RT and higher variability of RT (dominant hand (ms) = 670 vs 560, p = .04; nondominant hand = 820 vs 650, p = .003); omission errors = 1.95 vs 1.33, p = .004; RT related to IQ but neither to seizure severity, nor to duration of seizure disorder or of medication use [68].</td>
</tr>
<tr>
<td>Stroop Test</td>
<td>Selective attention, inhibition, executive functions</td>
<td>Response time, number of errors</td>
<td>Group with CAE: n = 31; focal impaired awareness seizures: n = 53; controls: n = 51 [69]</td>
<td>Genetic epilepsy: n = 57 of which n = 21 with GGE [70]</td>
</tr>
<tr>
<td>Test of Variables of Attention (TOVA)</td>
<td>Sustained attention, inhibitory control, impulsivity</td>
<td>Response time, commission errors, omission errors, postcommission response times, consistency of response, ADHD scores</td>
<td>Genetic epilepsy: n = 31 of which n = 53 with GGE; n = 57 of which n = 21 with GGE [70]</td>
<td>Results on n = 21 based on comparison with the normal mean of 100: Omission errors = 69.7 (38.2), RT = 90.2 (12.3) and RT variability = 84.7 (19.6), p = .006; Lower scores in all categories of TOVA, but in commission errors (impulsivity measure) [70].</td>
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<tr>
<td>D2 Test of Attention</td>
<td>Selective attention, concentration and visual discrimination</td>
<td>Commission and omission errors, RT, variability of responses</td>
<td>GGE: n = 15; focal epilepsy: n = 50; controls: n = 42 [71]</td>
<td>Mean of test scores on n = 15 and controls: 57 ± 27 vs 57 ± 40, no significant differences. Significance found in overall epilepsy duration and AED polytherapy associated with significantly worse performance than healthy controls [71].</td>
</tr>
<tr>
<td>EpiTrack Junior</td>
<td>Attention and executive functions</td>
<td>Verbal comprehension index, working memory index, processing speed index (10 subsets)</td>
<td>Group with CAE: n = 12</td>
<td>41% (n = 9) had unimpaired scores, 41% (n = 9) mild impairment, 18% (n = 4) significant impairment [75].</td>
</tr>
</tbody>
</table>

Note: Some of the studies included in this table use the previous nomenclature for epilepsy and epileptic seizures. To keep consistency with the definitions used in the text [2], we use the current nomenclature.

a "Genetic epilepsy" is “idiopathic epilepsy” in the referred study.

b GGE is “primary generalized epilepsy” in the referred study.

c "Focal impaired awareness seizures" is “complex partial seizures” in the referred study.
and category fluency, sustained and divided attention. In this case, it seems that attentional problems in CAE and JAE are present even when seizures are controlled [7,65]. In this regard, different results claim that monotherapy and polytherapy of AED have detrimental effects on children's cognitive functions [75,76]. Other studies conducted with the Attention Network Test (ANT) [53,66] and with “classical” tests for attention and EF, such as the Stroop Test and the Wisconsin card sorting test [69], reveal that, on average, children with GGE have an overall slower RT compared with healthy controls, indicating a significant deficit in their executive control.

An additional link between attention and absences lies in the high comorbidity between AE and ADHD. Childhood absence epilepsy manifests a 2.5- to 5.5-fold increased risk of developing ADHD [9,77]. In this population, the cases of ADHD are around 30–60% [9,34]. In one study [9], attention of children with CAE and children with ADHD was retrospectively compared using the advanced test of attention (ATA). As a result, the group with CAE made more omission errors, showing a greater impairment in selective attention. Childhood absence epilepsy also revealed a longer RT and a decreased RT variability than the group with ADHD. In the case of comorbidity between CAE and ADHD, a higher commission error rate and a greater RT variability was present, expressing an impairment of sustained attention deficit. Even though the comorbidity between the two conditions is remarkable, it is not clear which exact shared mechanism is responsible for the attentional impairment they divide [9,78].

These and other results on children with GGE and, specifically, with AE underline how this pediatric population usually manifests a longer RT and a significant impairment in sustained and divided attention. It should be taken into account that specific characteristics of the tests can provide different outcomes in patients with AE. Easier tasks (e.g., finger tapping [62]) are usually preserved during absences, while the demanding ones are more impaired, especially when they require verbal responsiveness [22,33]. Interestingly, the exhibition of stimuli interrupts the seizure if presented within 1 s from burst onset, whereas a less powerful effect occurs if the stimulus is presented after 3 s or more [79]. In some cases, stimulus presentation can, therefore, reduce the duration of the burst.

In sum, there is a critical impairment of attention in AE, but the actual link between attention and AE is far from being extensively understood. The types of methodologies adopted, the age of the groups involved, the existing comorbidities, and the treatments used represent a difficulty in defining a common view of the problem [9]. This is why we think it is crucial to evaluate a specific, practical aspect that may directly derive from the impairment of attention seen in AE: accidental injuries. This focus can give new, interesting research insights and can be applied for clinical indications too.

4.2. Accidental injuries related to attentional deficits in AE: is the risk higher?

The most harmful consequences of the impairment of attention during seizures are accidents: “any event resulting from a sudden unexpected cause leading to physical damage requiring medical attention or resulting in financial obligation” [80]. Several studies have assessed the correlation between seizures and injuries related to accidents [11–17,20], showing that the accidental lesions associated with epileptic events are mainly mild. The most common type of injuries related to seizures are soft-tissue lesions, followed by submersion injury, burns, fractures, head injuries, dental injuries, and motor vehicle accidents [81].

Two reviews discuss harmful casualties related to epileptic syndromes, among which also AE is present [81,82]. The nature and seriousness of seizure-related injuries vary according to the epileptic syndrome: generalized ictal activity, especially tonic–clonic, atonic, or myoclonic seizures, are considered a great risk factor for injuries [81,83]. Conventionally, the intractable types of epilepsies that persist in adulthood show higher rates of injuries [84]. Moreover, the frequency of the seizures has a relevant influence on accidents, together with the occurrence of interictal discharges. Indeed, the rate of accidents happening at home, at work, or in the street has been reported to be higher than average for the population with epilepsy, even when seizures are not manifested [80]. Furthermore, the side effects of antiepileptic medications, especially polytherapy, concur to the higher risk of accidents in this population [81,83]. Comorbidity of epilepsy with other neurological or psychiatric conditions (e.g., ADHD) and the presence of cognitive impairment are thought to highly increase the risk of injuries as well [15,81].

For patients with AE, the peculiar loss of awareness occurring during absences can generate an inability to react properly to external stimuli [81]. Most studies show that 30–35% of patients have sustained at least one injury caused by seizures [12,13,18,81]. Particularly, around 20% of patients with AE have reported to experience accidents during absences [5,11]. This risk has been estimated as 3% per person year [11]. Wirrell et al. [11] showed that patients with AE have a significant risk of injuries during absences, and their overall rate of accidents was higher even when not related to the occurrence of seizures. It is not trivial to generalize these results, given the discrepancies in the existing studies [83]: the choice of samples, the reliability of the sources, and the accuracy of patients' self-reported questionnaires. For example, a study on the prevalence of injuries carried out by the Canadian Community Health Service has shown that the difference in the risk of harmful events for people with self-reported epilepsy and the general population was not statistically significant, only the rate of hospital admission could be considered a relevant distinction between the two populations [16].

Motor vehicle accidents rate is higher in epilepsy, even though deathly accidents are rare [82]. Kirby and Sadler [19] found that in a specific Canadian province, the death associated with seizures accounted only for 1.2% of the total amount of seizures recorded at the local ER. These data suggest that the risk of injuries is higher during seizures, even though the difference with the general population is not remarkable [83]. However, the low rate of deathly fatalities reported may derive from an overall underreported incidence of these events. Indeed, the related literature is scarce, and the actual risk of fatal accidents may be higher. Given these contrasting results, there is a strong need for focused prospective studies, to define the peculiar consequences of injuries related to a specific epilepsy syndrome. For example, CAE and its associated risk during biking is an interesting issue to address, since the increasing popularity of cycling among young people. The results can be relevant both for research and clinical purposes.

The evidence on biking-related injuries is scarce. It is nevertheless especially important for the pediatric population. The mean number of bike accidents per 100 person-years in 59 children with CAE was more than two times larger than the control group (n = 61) with juvenile rheumatoid arthritis (5.2 and 2.0, respectively; p < .003) [11]. However, in Kirsch and colleagues [15], only a trend of higher cases of bicycle accidents was found, without any significant higher risk of biking-related injuries. This difference may result from the smaller sample in this study (n = 25). Further, all patients were free from cognitive or motor deficits, so that the children may showed different injuries probabilities compared with the sample used by Wirrell and colleagues [11]. In a large cohort of 198 newly diagnosed and untreated children with at least 2 seizures of any type (including 23 patients with CAE), no biking-related injuries were reported during the 12 months period of the study. These contradicting results reflect the need for more research, ideally assessing seizure risk tailored to the individual patient. For instance, measures of cortical excitability (e.g., EEG) and results of cognitive tests for attention can be merged in order to better investigate the relation of attention impairment and the risk of injuries in patients with AE.

5. Conclusion

In this review, we have discussed the characteristics and pathophysiology of AE and its relation to attention. Brain areas involved in AE and
attentional networks probably share common parts. We stress the importance for objective, reliable, and focused measures to assess the relation between AE and attention. Particular metrics, such as the risk related to biking in children with CAE or JAE, may be used in future studies to address the problem in a novel, original way and may also have a crucial impact for clinical actions.

Funding source declaration

Valentina Barone was funded by the Marie-Sklodowska-Curie grant agreement No 765298.

Declaration of competing interest

Michel J.A.M. van Putten is cofounder of Clinical Science Systems, manufacturer of clinical EEG software.

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