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Attention disorders in adults with epilepsy. Determinants and Therapeutic strategies

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Abstract

Cognitive consequences in epilepsy are often described in the following domains: verbal memory, language, executive functions, and attention. Attention is involved in all cognitive activities, and attention disorders (AD) are reported in patients with various neurological diseases. This paper proposes to define the concept of AD and its assessment, to consider their determinants in epilepsy and potential therapies (drug or not).

ADs are reported in new onset epilepsy, generalized epilepsy of presumed genetic origin, and in focal epilepsy. In focal epilepsy, alertness and divided attention impairment are observed and seem to improve after successful curative surgery. Additional studies are needed to assess the prevalence and nature of AD related to status epilepticus.

In the field of therapeutic strategies, anti-epileptic drugs show an impact on AD. Effects of antidepressive drug therapy are not reported, as well as psychotherapy. Cognitive rehabilitation on AD is a promising therapeutic intervention but specific studies are needed to assess its efficacy.

Introduction

Epilepsy is a “*disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition*” [1] Cognitive consequences in epilepsy are often described in verbal memory, language, and/or executive functions [2], but attention is rarely exhaustively studied. Attention is involved in all cognitive activities, and attention disorders (AD) are reported in patients with various neurological diseases [3, 4, 5]. A systemic review and a consensus from the ILAE have been recently published on diagnosis, screening and management of ADHD in children with epilepsy [6]. So, this opinion paper proposes to define the concept of AD and its assessment in adults with epilepsy, to consider their determinants and therapies (drug or not).

Attention: definition and assessment

Attention is a complex process, with cognitive and behavioral features. In the literature, many definitions are available. ADs are linked with attention deficit /hyperactivity disorder (ADHD). Criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [7] include six or more inattention and/or six or more hyperactivity-impulsivity symptoms in more than one situational context. In this review, we consider cognitive features of AD, not ADHD.

The first definition of attention was proposed by William James in 1890: “*Everyone knows what attention is. It is the taking possession by the mind in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thoughts...It implies withdrawal from some things in order to deal effectively with others*”. This definition is still topical. The current concept of attention comprises four dimensions: sustained attention, selective attention, divided attention, alertness [8]. More precisely, sustained attention refers to the ability to maintain vigilance over time; selective attention refers to goal-directed focus on task-relevant information while ignoring other irrelevant information; divided attention requires participants to perform two or more task simultaneously; alertness refers to reaction time. For example, when you drive, sustained attention is required throughout the way, selective attention is directed by events in the environment (car’s flashing lights, child crossing the street, ...), divided attention is required in dual tasks when you drive and listen to the radio simultaneously; and alertness is required when you wait at traffic lights. In daily life, these mechanisms are simultaneously involved all the time.

Several clinical tools are available to assess these different facets of attention. Attention depends on information processing speed, which must be controlled (TAP, subtest alert [9], WAIS 4, subtest Code [10], TMT A [11]). Attention assessment should not be restricted to information processing speed. Cancellation tasks are often used to briefly evaluate selective attention (i.e. d2 task [12]; Ruff 2&7 task [13]), however only the visual modality is explored.

Specific cognitive batteries have been designed to evaluate more precisely AD: TAP [9]; Vienna test System [14]; CANTAB [15]. The benefit of these specific batteries is to propose an exhaustive assessment of attention, with several subtests (sustained attention, selective attention, divided attention, alertness). The inconveniences of these tools are their duration (15 to 60 minutes) and their cost. Finally, attention is often confused with working memory and executive functions, because they require one or more of these attentional mechanisms. For example, Stroop Test [11], a verbal inhibition task requiring selective attention, is sometimes used by some authors as a marker of attention. Such interpretations must be considered with caution and we recommend to use at least one specific attentional test. D2 [12] task allows a brief assessment of selective attention (5 minutes with a tablet, see Figure 1). TAP battery [9] allows a complementary assessment of sustained attention, divided attention and alertness (see Figure 2).

Attention disorder determinants in adults with epilepsy

ILAE recommends to assess AD in adults with epilepsy [16]. Attention is modulated by several positive and negative factors. Some are specific and others not specific to epilepsy (cf Figure 3).

Non-specific determinants of attention

Attention is required to process external stimuli, so it depends very strongly on changes in the environment (noise, fatigue, etc.). AD's determinants not specific to epilepsy are motivation, sleep, mood, age, and/or neuropsychological profile. Depression and anxiety are associated with poorer performances across multiple domains, including attention, executive functioning, memory, and processing speed [17, 18].

Aging is accompanied by a decrease in attentional resources, and a greater sensitivity to interference, which leads to a decrease of behavioral performance in the elderly facing

multiple simultaneous tasks [19]. Importantly, attention is also linked to the global neuropsychological profile of the patient reflecting a reciprocal interdependency.

Specific to adults with epilepsy?

ADs are frequent in epilepsy, and have been reported in idiopathic generalized epilepsy (IGE), focal epilepsy, and new onset epilepsy [20]. However most of these studies have assessed only one of the four dimensions of attention. Seizure recurrence, inter-ictal activity, anti-epileptic drugs, focus location and disease duration can be considered as potential specific determining factors of AD.

In a recent study focusing on IGE, 36 patients with IGE, 38 first-degree relatives, and 40 healthy controls were examined using a battery of neuropsychological tests sensitive to sustained attention and frontal lobe dysfunction (executive function, nonverbal reasoning, verbal generativity, response inhibition, and working memory) [21]. Patients with IGE showed deficits predominating in sustained attention but involving also various executive functions (nonverbal reasoning, verbal generativity and working memory). Interestingly, non-epileptic and untreated relatives exhibited a parallel profile of cognitive abilities, with significant but less pronounced deficits. Authors suggested that this common cognitive profile could result from a common genetic trait independent of seizures or antiepileptic drugs. Conversely, the tendency of patients to demonstrate greater impairment in these tasks could be due to a combination of greater genetic contribution and/or factors related to seizures and/or treatment.

A study [22] proposed to assess AD in focal epilepsy (Temporal Lobe Epilepsy: TLE) with an exhaustive assessment including sustained attention, selective attention and short-term memory. Fourteen TLE surgery candidates (4 left TLE, 10 right TLE) achieved the comprehensive neuropsychological assessment. Impairment was reported in short term memory, and selective attention, with a preservation of sustained attention. These findings suggest that attentional impairment in TLE was not global and could be limited to a single dimension, for instance selective attention. The greatest deficits appear to be on tasks that require a high load of processing resources. In contrast, sustained attention is less compromised and the capacity to allocate cognitive resources appears to be normal in patients with TLE.

Impact of side of lesion, seizure outcome and interictal epileptiform discharges (IEDs) on attention after surgery were explored with 94 patients with left (n=50) and right (n=44) intractable mesial TLE [23]. Selective attention was evaluated with Go/No-Go test (TEA),

divided attention with TEA subtest and focused attention with a cancellation task (D2). In selective attention, RTLE patients produced significantly more errors. In divided-attention, postoperatively seizure-free patients were significantly faster than patients with recurring seizures. In addition, patients who continued to present IEDs in the one-year postoperative routine EEG tended to have a slower performance and a higher omission rate, regardless of the time of examination and their seizure outcome. Results in focused attention showed a significant effect of seizure outcome, and a significant two-way interaction between side of surgery and time of examination. The LTLE group, but not the RTLE group improved postoperatively. Results could suggest that AD may not only be attributed to unfavorable seizure outcome after surgery, but also to the persistence of IED activity. In addition, variables measuring basal selective attention reflect the importance of the functional integrity of the non-dominant temporal lobe and its interaction with the large, right-sided frontoparietal network which underlies basal sustained and selective attention. This study suggested a link between several variables on post-surgical attention outcome (persisting IED activity, seizure outcome, location side ...). Post-surgical improvement of attention was also described in other studies using cancellation task [24], and interpreted as the result of a general cognitive improvement, as mentioned in a previous report [25]. Surprisingly a study the neuropsychological profile of FLE and TLE showed a greater impairment of executive functions but not of selective attention in FLE than in TLE suggesting that ADs are not specific to a single epileptogenic zone localization [26]

Therapeutic strategy

Therapeutic strategies include a drug and a psychotherapeutic approach. The drug approach corresponds to AED and anti-depressive drug therapy. The psychotherapeutic approach corresponds to cognitive rehabilitation and psychotherapy.

Anti-epileptic drug therapy

Combination of antiepileptic drugs contributes to the emergence of cognitive effects [27], and difference of these effects according to the molecules are observed. Each molecule has a specific profile. Epitrack [27] is the most common tool to assess cognitive impact of AED. Some molecules have no interaction with cognitive performance, some could improve

it, or could impair it in a specific field. Potential attentional effects of AED are summarized in table 1 [27, 28].

Cognitive risk is also major with combinations of multiple AED [29]. Witt et al. [30] suggested that numerous AEDs appears to impair all cognitive functions, especially attentional / executive functions and, to a lesser extent, memory functions. These results are observed with Epitrack score, but Epitrack does not specifically measure patients' attentional capacities. The benefit/risk balance of AED is very difficult to assess. Some drugs may cause direct negative effects, but in contrast, the control of epileptic seizures may have a positive effect on mood and associated psychiatric disorders and could also independently lead to an improvement of attention. Some molecules may have a direct positive effect on cognitive performance by improving alertness and cognitive abilities [27]. Negative effects of AED on attention could depend on the used posology and can therefore be improved by pre and post-treatment introduction monitoring and trying to find the lowest efficient dosage. In any case, cognitive side effects of AED in adults have been shown to be reversible after cessation [31, 32].

Antidepressive drug therapy

The incidence of depression is five to 20 times higher in patients with epilepsy than in the general population [33]. Numerous studies have investigated cognitive functions in depression, including attention, processing speed, executive function, and verbal memory. Effects of antidepressive drug therapy (ADT) on attention in patients with epilepsy are not reported. Effects of ADT on cognition are described in depressed patient [34], more precisely in attention, improvement is reported but with no specific task. Altogether AD, depression, and epilepsy are confused, and care of these three axes is crucial. Close collaboration between psychiatrists, neurologists and neuropsychologists is necessary in order to stop the vicious circle of mutual aggravation of one pathology by the other. One must not be resigned to one's disorders in order to progress towards a satisfactory therapeutic balance.

Cognitive rehabilitation

Cognitive rehabilitation (CR) is developed in neurological pathologies. AD rehabilitation programs have been developed mostly on numeric supports implementing restauration technics. The main objectives of such software (Rehacom, CogniPlus, PRESCO,...) are to manage intensity and specificity of attention.

In epilepsy, despite the knowledge of cognitive disorders and the large number of patients, very few studies have been conducted. A first study [35] mentioned that “*a comprehensive cognitive rehabilitation approach involves the increment of the individual’s awareness of his or her cognitive deficits and the subsequent retraining of those cognitive functions that were specifically impaired, or the teaching of compensatory strategies*”. Two cognitive methods have been proposed in patients with focal seizure, according to their cognitive impairment: restorative method for AD, compensatory method for verbal memory impairment. Here, the first approach is presented. Attentional assessment was exhaustive, with visual alertness, acoustic alertness, focused attention, divided attention, selective attention, and vigilance. Enrolled patients included had a poor performance on at least two of the six attentional dimensions. Divided attention capacity was affected in most patients. Six weekly sessions were administered. Positive effects on neuropsychological outcome related to the Retraining Method were reported in divided-attention (on omissions). Six months later, remaining effects were found, suggesting that benefits were sustained over a long period of time after the intervention. This might indicate that patients have incorporated these new methods into their daily-life functioning. Supplementary analyses demonstrated that patients who still had seizures benefited more from either program than the seizure-free patients. Authors suggest that cognitive rehabilitation programs are effective for patients with focal seizures and attention deficits should be added into comprehensive care programs.

In a second study [36], two groups of patients who underwent temporal lobe resection, were assigned to two arms with ($n = 55$) and without ($n = 57$) postoperative rehabilitation. They were evaluated with respect to memory and attention before and three months after temporal lobe surgery. RehaCom software was used for rehabilitation of AD. The study showed that attentional performance improved independent of cognitive training. Previous research has demonstrated that nonmemory function deficits obviously have the potential to recover after surgery without any interventions, an effect that has been interpreted in terms of a release due to control of epileptic activity.

So, CR in AD with epilepsy is not really developed, and more studies should be considered, to assess CR effects in patients with epilepsy, and to determine which patients are best responsive to these interventions (focal seizure?) and when as regard as the time of surgery (pre or postoperatively).

Psychotherapy

As previously mentioned, depression and anxiety are associated with cognitive impairment including attention, executive functioning, memory, and processing speed [17, 18]. The principles of depressive and anxious comorbidities care are similar in patients with epilepsy and in patients without epilepsy, with a combination of pharmacological therapies and psychotherapy such as cognitive and behavioral therapies (CBT).

CBTs have been shown to be effective in anxiety and depressive disorders on these symptoms but not on the frequency of seizures. CBTs of anxiety disorders focus on the perception of stress and their interpretation of anxiety symptoms. Thus in epilepsy, they are particularly interesting in the treatment of the specific phobia of epileptic seizures in order to reduce the anticipatory anxiety seizures and improve the level of anxiety, depressive symptoms and quality of life [37].

Conclusion

Cognitive disorders such as verbal memory and language have been extensively described in patients with epilepsy. In contrast, few studies have specifically explored AD, separately from executive functions and speed processing. ADs have been reported in new onset epilepsy, idiopathic generalized epilepsy, and in focal epilepsy. AD seems to decrease after successful surgery. In focal epilepsy, ADs predominate on selective attention and divided attention. More studies are needed to specify prevalence and nature of AD, related to epileptic status.

In the field of therapeutic strategies, anti-epileptic drugs show an impact on AD. More studies should be conducted to explore specifically their specific impact on the four dimensions of attention. The efficacy of antidepressants as well as psychotherapy on attention have not been specifically studied but a benefit can be expected through the indirect effect on depressive and anxiety disorders. Cognitive rehabilitation of attention disorder seems promising but additional studies are mandatory to demonstrate its efficacy.

Conflicts of interest

The authors declare that they have no conflict of interest concerning this article.

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<p>Selective attention</p> <p>D2</p> <p>Test duration: 5 minutes</p>	
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Figure 1. D2-R task of selective attention

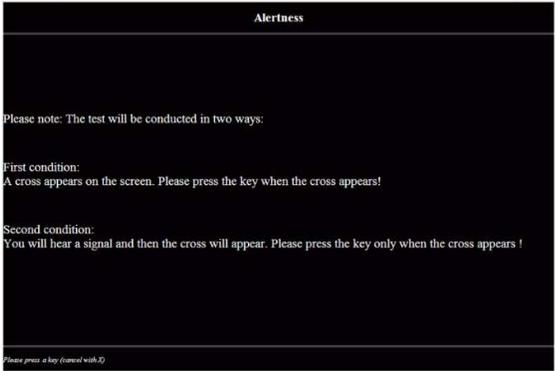
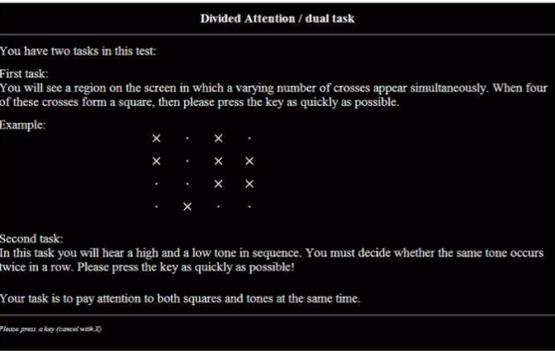
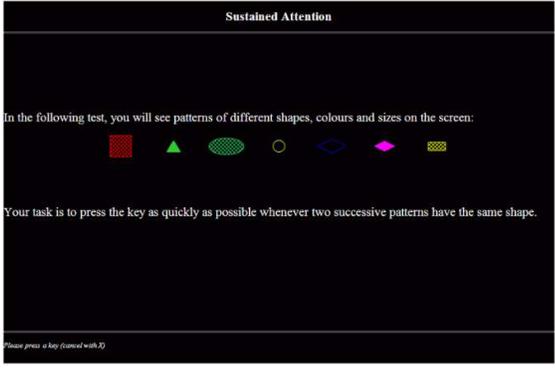
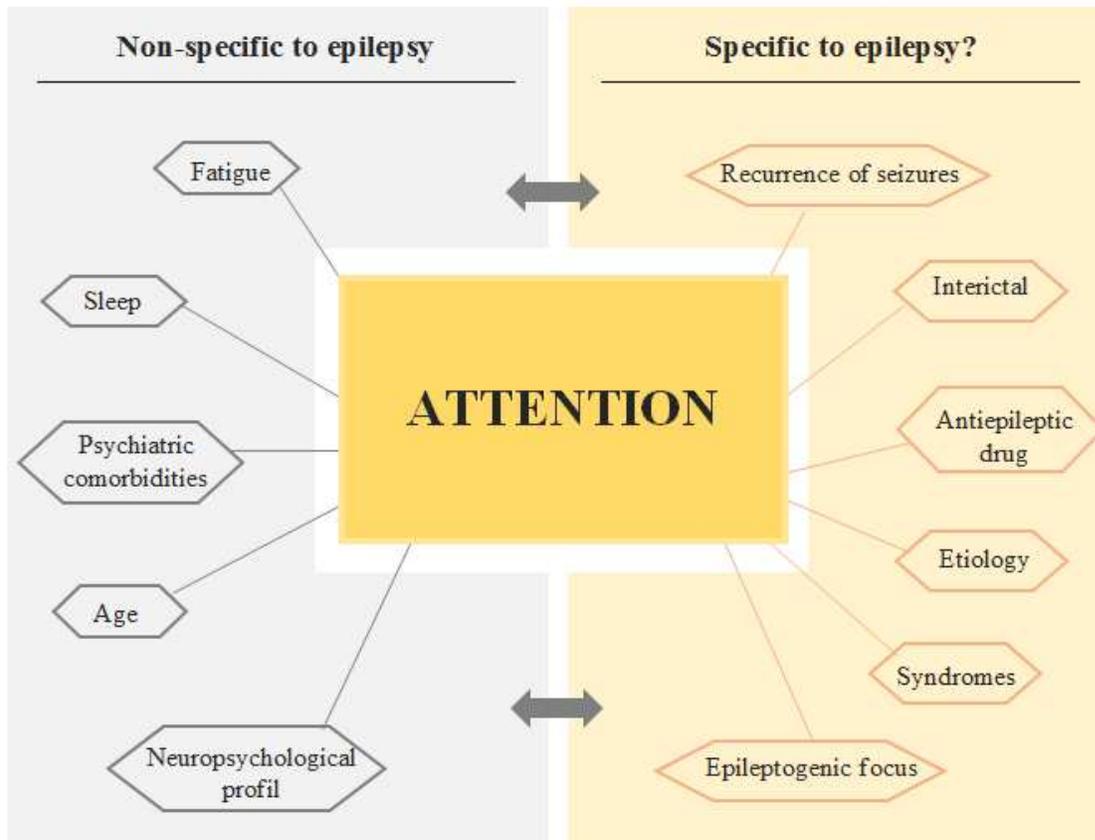
Subtests	Examples
<p style="text-align: center;">Alertness</p> <p style="text-align: center;">TAP 2.2 – Alertness</p> <p style="text-align: center;">Test duration: 5 minutes</p>	
<p style="text-align: center;">Divided attention</p> <p style="text-align: center;">TAP 2.2 – Divided attention</p> <p style="text-align: center;">Test duration: 6 minutes</p>	
<p style="text-align: center;">Sustained attention</p> <p style="text-align: center;">TAP 2.2 – Sustained attention</p> <p style="text-align: center;">Test duration: 15 minutes</p>	

Figure 2. TAP Battery

Figure 3. Determinants specific or not to epilepsy



	Attention and executive functions
Lamotrigine	0/↑
Lacosamide	0
Levetiracetam	0/↑
Oxcarbamazepine	(↓)/(↑)
Rufinamide	0
Eslicarbazepine	0
Vigabatrin	0
Perampanel	0
Stiripentol	?
Pregabalin	0
Valproic Acid	↓
Tiagabine	0
Ethosuximide	(↓)
Felbamate	(↓)
Gabapentine	0/(↓) ou (↑)
Clobazam	↓
Carbamazepine	↓
Zonisamide	(↓)
Phenobarbital	↓
Phenytoin	↓
Topiramate	↓

↓ : negative effect ; ↑ : positive effect ; () : possible effect ; 0 : no effect ; ?: data insufficient

Table 1: Effects of AED on Attention and Executive functions