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REVIEW

Impact of focal interictal epileptiform discharges on behaviour and cognition in children

Impact des décharges épileptiformes focales sur le comportement et les fonctions cognitives chez l'enfant

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Summary It is hypothesised that focal interictal epileptiform discharges (IED) may exert a deleterious effect on behaviour and cognition in children. This hypothesis is supported by the abnormally high prevalence of IED in several developmental disorders, like specific language impairment, and of cognitive and behavioural deficits in epileptic children after excluding confounding factors such as underlying structural brain lesions, drug effects, or the occurrence of frequent or prolonged epileptic seizures. Neurophysiological and functional neuroimaging evidence suggests that IED may impact cognition through either transient effects on brain processing mechanisms, or through more long-lasting effects leading to prolonged inhibition of brain areas distant from but connected with the epileptic focus (i.e. remote inhibition effect). Sustained IED may also impair sleep-related learning consolidation processes. Nowadays, the benefits of anti-epileptic treatment aimed at reducing IED are not established except in specific situations like epileptic encephalopathies with continuous spike and waves during slow-wave sleep. Well-designed pharmacological studies are still necessary to address this issue.
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MOTS CLÉS
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Résumé Il existe un faisceau d'arguments en faveur du concept selon lequel les décharges épileptiformes intercritiques (DEI) focales peuvent exercer un effet délétère sur le comportement et la cognition chez l'enfant. Ces arguments sont, d'une part, la prévalence élevée de DEI dans certaines pathologies du développement, comme la dysphasie développementale, et, d'autre part, la prévalence élevée de déficits cognitifs et de troubles du comportement chez les enfants épileptiques après exclusion de facteurs confondants comme une lésion structurelle cérébrale sous-jacente, un effet médicamenteux, ou la survenue de crises épileptiques fréquentes ou prolongées. Les données neurophysiologiques et de neuro-imagerie fonctionnelle suggèrent que les DEI peuvent inhiber certains processus cognitifs cérébraux de façon très transitoire mais également de façon prolongée. Ces effets prolongés des DEI consistent notamment en une inhibition de régions cérébrales distantes connectées au foyer épileptique et en une altération de la consolidation des apprentissages au cours du sommeil. Le bénéfice d'un traitement médicamenteux visant à réduire les DEI n'est actuellement pas établi sauf dans certaines situations particulières comme l'encéphalopathie épileptique avec pointe-ondes continues du sommeil. Cette question doit être abordée par la réalisation d'études médicamenteuses bien conduites.
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Introduction

A deleterious impact of focal interictal epileptiform discharges (IED) on behaviour and cognition in children has been presumed for a long time. This hypothesis of IED-induced cognitive and behavioural deficit is mostly supported by two sets of studies.

First, the prevalence of focal IED in the electroencephalogram (EEG) of cohorts of non-epileptic children with developmental disorders of behaviour or cognition has been reported significantly higher than the 3 to 6% prevalence observed in two main normative paediatric studies [7,22]. Studies performed in children with specific language impairment reported an incidence of IED during sleep ranging from 30 to 80% [20,21,43]. In children with an attention-deficit hyperactivity disorder, studies reported an IED incidence ranging from 6% on wake EEG [27,50] to more than 50% when sleep EEG was recorded [59]. However, it should be kept in mind that the two aforementioned normative studies were performed during a 20-minute wake period [7,22]. Data on the incidence of IED in long-term EEG including sleep recordings are scarce in normal children. Although it may be hypothesised that IED incidence would be higher in these conditions than in a mere short-term wake session, this prediction was not verified by Picard et al. who found an IED incidence of 5% during sleep in a group of 20 normal children [43].

Second, several studies aimed at identifying a possible contribution of IED to cognitive and behavioural problems eventually found in epileptic children. The difficulty in this situation is to segregate the effects of IED from the effects of other confounding variables, such as the underlying aetiology (genetic predisposition versus structural or metabolic brain lesion), the repetition of overt seizures, and the use of anti-epileptic drugs (AED). Still, a prospective study aimed at evaluating the contribution of these various factors on neuropsychological results collected within 3 months of the first recognized seizure identified the presence of IED on EEG as a risk factor for cognitive deficit [23]. The impact of IED on behaviour and cognition is particularly interesting to study in the context of idiopathic focal epilepsies for several reasons. First, these epilepsies expressed only during a particular period of the life span are not associated with any structural brain lesion. Second, seizures are usually infrequent and of brief duration, making the use of AED often unnecessary. Third, children with focal idiopathic epilepsy usually have very frequent IED in their EEG, still present in the awake state but more abundant during non-rapid eye movements (NREM) sleep. Three forms of focal idiopathic (genetic) epilepsy have been recognized by the International League Against Epilepsy (ILAE) in the now quite old classification of epileptic syndromes: benign epilepsy with centrotemporal spikes (BECTS), also called rolandic epilepsy, benign childhood epilepsy with occipital paroxysms (BCEOP), and reading epilepsy [11]. The term ''benign'' here refers to the fact that patients usually have a favourable outcome, not only for seizures but also for behaviour and cognition. However, a substantial number of BECTS children present heterogeneous cognitive deficits affecting language and memory functions that are associated with the intensity of interictal spiking and evolve to recovery with EEG normalization [5,18,35,37,39]. This suggests that these deficits are associated with the presence of IED. Since the publication of the ILAE classification of epileptic syndromes in 1989, it has appeared that a subgroup of focal idiopathic epilepsy evolves to epileptic encephalopathies (EE) with continuous spike and waves during slow-wave sleep (CSWS). This epileptic syndrome associates severe global or task-specific cognitive regressions with almost continuous and diffuse IED during slow-wave sleep but also other stages of NREM sleep (stages 1 and 2). Some CSWS cases are symptomatic of a focal brain lesion. The existence of an idiopathic subgroup is supported by reported cases with normal cerebral magnetic resonance imaging (MRI) showing evolution from BECTS to EE with CSWS, by transitory cases so-called ''atypical rolandic epilepsy'', and by the possible coexistence of EE with CSWS and BECTS within the same family [13,24,53,63,67]. This suggests that BECTS and EE with CSWS are at the edges of a spectrum where the most frequent and diffuse IED during slow-wave sleep result in the more severe behavioural and

cognitive deficits. The impact of IED on cognitive deficits is recognized in EE with CSWS as normalization of sleep EEG with drugs, particularly corticosteroids, results in considerable cognitive improvements [2,9].

Despite this literature supporting a negative impact of IED on behaviour and cognition, controlled-studies designed to evaluate the effect of an AED aimed to reduce IED are still lacking. Only one randomized placebo-controlled study showed that treatment of IED can improve behaviour in epileptic children [46]. As the use of AED is also an independent risk factor for cognitive deficits in epileptic children [23], AED are primary prescribed to prevent seizure recurrences and not to treat IED, except in special situations like EE with CSWS. A better understanding of the pathophysiology of IED-induced cognitive deficits is thus crucial. In this respect, two non-exclusive hypotheses are proposed. The first account hypothesises that each IED will induce a transient inhibition of brain networks. The second hypothesis proposes more long-lasting effects of IED on brain functioning and plasticity. These two hypotheses will be discussed in the following sections.

Transient effects of interictal epileptiform discharges

Interictal spikes may produce transient cognitive effects identified behaviourally using sophisticated neuropsychological evaluation under EEG control. This phenomenon is called transient cognitive impairment (TCI) and was first described by Aarts et al. in 1984 [1]. Epileptic patients underwent verbal and visuo-spatial tasks under EEG control, and association of error with IED defined TCI. These authors found TCI in about 50% of patients, and an association between IED laterality and the type of task, errors on verbal task being associated with left-sided IED and on nonverbal task with right-sided IED. Shewmon and Erwin studied the temporal profile of IED-related transient effects by measuring reaction times after presentation of visual stimuli in two patients with abundant posterior focal spike-waves, and showed that this effect started 100—200 ms before the spike to end with the termination of the slow-wave [58]. Because the maximal intensity of the dysfunction occurred around the middle of the slow-wave and correlated with the size of the slow-wave but not with the spike, these authors hypothesised that TCI was not merely related to the inhibition of the cortical region that generated the spike but also by surrounding connected areas that generated the after-coming slow-wave. Transient decrease in neuronal activity recorded from cortex surrounding an epileptic focus was confirmed using optical imaging in an animal model of focal IED [56]. However, further behavioural studies aimed to identify TCI in focal epilepsies failed to replicate this TCI phenomenon in a large majority of patients [3]. Given these results, Seri et al. hypothesised that the low sensitivity of neuropsychological tasks to demonstrate an altered response concomitant to the occurrence of a focal IED could be due to the very short duration of IED and to the large distribution of neural networks involved in neuropsychological tasks. They therefore proposed to search for altered evoked neurophysiological responses triggered by IED [57]. Using this methodology, these authors found a significant effect of focal IED on auditory evoked responses in six patients with acquired auditory agnosia and IED, i.e. Landau-Kleffner syndrome (LKS), suggesting a direct effect of IED on auditory cortical functioning [57]. More recently, the combination of EEG and functional magnetic resonance imaging (fMRI) has been used to characterise the metabolic correlates of IED. EEG-fMRI takes advantage of the blood oxygen level dependent (BOLD) effect to identify haemodynamic changes in the brain correlated with pathological EEG activity, with a temporal resolution on the order of the second [26]. Studies performed in adults with temporal lobe epilepsy have shown that focal IED are associated with complex haemodynamic changes [31]. If activation is usually seen within the epileptic focus, deactivation may also occur. Moreover, activation and deactivation may be seen in remote cortical and sub-cortical structures, suggesting an effect of IED on distant synaptically connected regions. The neurophysiological correlates of deactivations seen on EEG-fMRI are still debatable. Indeed, deactivation could be related to a GABAergic inhibition requiring little energy and leading to reduced action-potential activity, but also to a deafferentation leading to reduced synaptic activity [31]. EEG-fMRI performed in a child with CSWS disclosed a combination of activation in the presumed epileptogenic zone, and extensive deactivation in lateral and medial frontoparietal cortices and posterior cingulate gyrus, that was interpreted as reflecting an impact of IED on normal brain function leading to neuropsychological regression [14]. Analyses performed at the group level in adults with temporal lobe epilepsy [33] and in children with CSWS [60] also favoured this hypothesis, showing significant deactivation in several regions participating to the default mode network (precuneus, medial frontal, and temporoparietal cortices). The default mode network is composed by connected brain structures that are active when normal subjects are at rest and deactivated when they engage in a task [47]. Thus, IED-related inhibition of the default mode network would lead to a decrease in awareness.

In conclusion, several studies have shown that IED may have transient consequences on brain functioning that may be evidenced behaviourally or using evoked potentials and EEG-fMRI. IED could result in cognitive deficits in sustaining functionally inappropriate synaptic cortico-cortical arrangements in a critical period for development of associative cortices, as hypothesised by Morrell et al. [38]. However, considering the difficulties to clinically identify TCI, it remains difficult to conceive that it is only through the repetition of transient time-locked effects that IED contribute to sustained cognitive deficits, suggesting further long-lasting effects.

Long-lasting effects of interictal epileptiform discharges on brain functioning and plasticity

Positron emission tomography (PET) using [18F]-fluorodeoxyglucose (FDG) is routinely used in the context of presurgical evaluation of refractory focal epilepsy: most patients show focal hypometabolism that frequently extends beyond the epileptogenic zone and is mainly related to both neuronal loss and deafferentation [19]. In children with idiopathic focal epilepsy, FDG-PET provides a

way to study long-lasting effects of IED on brain functioning at rest. Indeed, the absence of a cerebral lesion precludes focal hypometabolism as a consequence of neuronal loss. Moreover, as the temporal resolution of FDG-PET is very low when compared with EEG-fMRI, episodic focal interictal spikes are not expected to produce any significant metabolic changes. Accordingly, investigations performed in children with typical BECTS when awake in the interictal state did not reveal any significant regional change in cerebral glucose metabolism [66]. At variance, most cases of children having EE with CSWS and normal MRI, when investigated in the same conditions with comparable amount of IED during PET acquisition than BECTS patients, showed deeply abnormal patterns of regional glucose metabolism [12]. As the main differences between these two groups of patients were the presence of CSWS patterns during the night that preceded PET scanning and the acquired cognitive or behavioural deficits, it was hypothesised that metabolic changes could be related to abundant IED during sleep, eventually disclosing brain regions both involved in epileptic activity and cognitive deficits. In this respect, one abnormal metabolic pattern was an association of regional hypermetabolism in the epileptogenic zone with hypometabolism in distinct, remote brain areas. At the group level, those patients showed centroparietal hypermetabolism and prefrontal hypometabolism. This finding was interpreted as a phenomenon of remote inhibition of the prefrontal hypometabolic regions by highly epileptogenic and hypermetabolic posterior cortex. This hypothesis was supported by effective connectivity analyses that demonstrated the existence of significant changes in the metabolic relationship between these brain areas in this group of children compared to a control group. Based on these results, we proposed that in EE with CSWS, the cortical regions concerned by intense interictal spiking during sleep remain hypermetabolic at the awake state and inhibit remotely connected brain areas. According to the concept of remote inhibition, cognitive deficits are related to dysfunction of both hypermetabolism at the site of the epileptic foci and hypometabolism in distant and connected brain areas [12,15,16]. Normalization of the regional metabolism and effective connectivity changes after regression of the CSWS pattern using drugs provided further evidence that the intense epileptic activity occurring in NREM stages of sleep in those patients impacted on brain functioning during the awake state [15].

It has also been hypothesised that the abundant IED during NREM sleep in EE with CSWS could interfere with the sleep-dependent physiological processes of neuronal plasticity supporting memory consolidation for recently learned information [10,29,64]. Memory consolidation refers to a dynamic longitudinal time-dependent process converting labile memory traces into more permanent and/or enhanced forms [36]. These transformations are made possible by brain plasticity, i.e. the capacity of the brain to modify its structure and function over time [32]. Studies performed in adults suggest that both REM and NREM sleep stages participate to memory consolidation. Whereas some studies suggest that the different stages of sleep are involved in the consolidation of specific memory systems, with consolidation of declarative memory mainly occurring during slow-wave sleep and of procedural memories during REM sleep, other studies suggest that adequate succession of all stages of sleep is mandatory for some memories to consolidate [44,61,68]. In children, it has been demonstrated that sleep also plays an important role in the consolidation of declarative memory, but its effect on the consolidation of procedural memories is less clear [4,45,69]. Besides sleep-dependent consolidation, recent animal and human data also indicate that post-training awake periods also may achieve the necessary conditions to consolidate novel memories in the nervous system [8,30,42,51], cognition- and consolidation-related cerebral activity being additionally modulated by complex interactions between circadian and homeostatic regulatory processes [17,52,54,55]. In healthy adults, neuroimaging studies have shown delayed reactivation of learning-related activity during post-training sleep [41,48] and awake [42] periods, followed by transfer from early hippocampal activity toward delayed prefrontal [25,62] and basal ganglia [40,49] activity days to months later. At the cellular level, early reactivation during sleep of the cortical regions involved in a specific task learned when awake could be expressed by an increase of synaptic strength [28] and by bursts of gamma oscillations [34]. In epileptic patients, memory consolidation has not been extensively studied. A study performed in adult epileptic patients showed that those patients with a left temporal epileptic focus have impaired long-term retention for a verbal memory task despite normal learning and short-term retention levels [6]. In childhood idiopathic focal epilepsies, we addressed recently the question of sleep-related declarative memory consolidation in studying four epileptic children (one case of BECTS, one case of benign childhood epilepsy with occipital paroxysms, and two cases of EE with CSWS) and an age-matched control group using a sleep-dependent word-pairs learning task [65]. In patients, but not in healthy controls, recall performance significantly decreased overnight, suggesting impairment in sleep-related declarative memory consolidation. Hydrocortisone treatment in one patient with EE with CSWS resulted in normalization of the sleep EEG together with normalization of overnight memory performance, which was not the case in the other EE/CSWS patient whose sleep EEG was only partially improved. These preliminary results therefore suggest that IED in idiopathic focal epilepsies may disrupt the brain processes underlying sleep-related memory consolidation, a hypothesis that should be supported by further studies.

Conclusions

There has been increasing evidence for an impact of IED on behaviour and cognition over the last decade. However, many questions concerning the pathophysiology and treatment of IED-induced deficits remain unanswered. In particular, the risk-to-benefit ratio of treating patients with a drug aimed at reducing IED still remains unknown in most clinical situations. Well-designed pharmacological studies are warranted to address these crucial questions.

Disclosure of interest

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

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