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Review

Interictal epileptiform discharge effects on neuropsychological assessment and epilepsy surgical planning

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ABSTRACT

Both animal research and human research suggest that interictal epileptiform discharges (IEDs) may affect cognition, although the significance of such findings remains controversial. We review a wide range of literature with bearing on this topic and present relevant epilepsy surgery cases, which suggest that the effects of IEDs may be substantial and informative for surgical planning. In the first case, we present a patient with epilepsy with left anterior temporal lobe (TL) seizure onset who experienced frequent IEDs during preoperative neuropsychological assessment. Cognitive results strongly lateralized to the left TL. Because the patient failed performance validity tests and appeared amnestic for verbal materials inconsistent with his work history, selected neuropsychological tests were repeated 6 weeks later. Scores improved one to two standard deviations over the initial evaluation and because of this improvement, were only mildly suggestive of left TL impairment. The second case involves another patient with documented left TL epilepsy who experienced epileptiform activity while undergoing neurocognitive testing and simultaneous ambulatory EEG recording. This patient's verbal memory performance was impaired during the period that IEDs were present but near normal when such activity was absent. Overall, although the presence of IEDs may be helpful in confirming laterality of seizure onset, frequent IEDs might disrupt focal cognitive functions and distort accurate measurement of neuropsychological ability, interfering with accurate characterization of surgical risks and benefits. Such transient effects on daily performance may also contribute to significant functional compromise. We include a discussion of the manner in which IED effects during presurgical assessment can hinder individual patient presurgical planning as well as distort outcome research (e.g., IEDs occurring during presurgical assessment may lead to an underestimation of postoperative neuropsychological decline).

It has been controversial whether interictal epileptiform discharges (IEDs) affect cognitive function [1–3], yet growing evidence suggests that they may [4–6]. We review a broad array of studies with bearing on this topic, and we report two cases whose preoperative neuropsychological evaluations were meaningfully affected by IEDs and in whom significant performance improvements were observed when evaluated without active IEDs. These cases contribute to the review by highlighting the importance of identifying relevant IEDs during preoperative neuropsychological testing and demonstrating how IEDs may influence individual patient surgical decision-making while also affecting reports describing the incidence of postsurgical neuropsychological change.

1. Research demonstrating the effects of interictal epileptiform discharges on cognition and behavior

While research examining the effects of IEDs on cognition and behavior has produced mixed results over the years, clearer results have come with use of paradigms employing tasks sensitive to dysfunction *specific* to the brain regions from which the epileptiform activity arises [3,7]. Some studies also demonstrate that effects on function worsen with longer duration of IED discharges [4,8].

Several studies have reported a relationship between IEDs and various aspects of cognition and behavior. One of the earliest reports demonstrated that reaction time was slowed in individuals during episodes of interictal activity in the absence of seizures, termed "subclinical epileptic activity" [9]. More recently, Aldenkamp and colleagues showed that patients with epilepsy experiencing IEDs during as little as 1% of the cognitive assessment period performed significantly slower on tasks [10]. A

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number of additional studies have reported "transient cognitive impairment," a temporary disruption of general cognitive functions with IEDs [9,11,12]. A limitation of this area of research has been that EEG results were often not simultaneous with behavioral performance. Research has sometimes found transient disruption of very specific functions, highlighting the focality of the effects of IEDs. For example, impaired performance on visuospatial/visuomotor tasks has been observed with interictal spikes involving the right cerebral hemisphere [7]. Similarly, Binnie et al. [13] reported a pattern of material-specific memory deficits involving left or right hemisphere IEDs. Generalized spike-wave discharges also lead to brief disruptions of cognition [14], usually with a disruption of reaction time and brief amnesia for the duration of the discharge [15].

Some studies have shown that IEDs can affect complex behavioral routines and aspects of everyday functioning. For example, Kasteleijn-Nolst Trenite et al. [16] found that patients with epilepsy made driving errors during an on-road simulation test when they experience interictal epileptiform activity. Similarly, Eurocontrol has required all applicants for air traffic control training programs to undergo a screening EEG since the mid-1990s. This screening was implemented after an applicant without a history of seizures made mistakes tied to the occurrence of generalized epileptiform discharges [17]. Each year, several applicants are reportedly excluded from further training based on abnormal EEG findings.

1.1. Indirect evidence for the effect of IEDs on cognition and behavior

1.1.1. Nocturnal IEDs

Several childhood epilepsy syndromes exhibit predominantly nocturnal epileptiform activity (e.g., Landau–Kleffner syndrome, benign childhood epilepsy with centrotemporal spikes [BCECTS]) [18] and are associated with mild cognitive deficits, learning disorders, and behavioral issues. Several studies demonstrate that a high nocturnal spike index is associated with poor cognitive function [19,20], although the relationship between the presence of spikes and specific cognitive functions is less clear. Several studies report a correlation between the presence of nocturnal IEDs or seizures and degree of language impairment [21,22].

Nocturnal IEDs have been mostly studied in patients with BCECTS, as these patients usually experience epileptiform activity during sleep and are typically on AED monotherapy or no drug at all [23]. Various studies have demonstrated that children with BCECTS tend to have lower general intellectual functioning and mild dysfunction across a variety of neurocognitive domains (e.g., aspects of executive control processing, language, verbal academic achievement, auditory/verbal memory and learning, and verbal fluency) compared with healthy control subjects [21,24,25]. Overall, those with a high frequency of localized IEDs perform worse than those with low rates of activity [22,26]. Some studies suggest that, upon reaching adulthood, at which age BCECTS typically resolves, neurocognitive function may not differ significantly from healthy controls [27], suggesting that nocturnal epileptiform activity drives the dysfunction observed during the active phase of the disorder. However, some recent studies suggest persisting academic difficulties and other functional compromise in these patients even when cognitive functioning has stabilized [28–31].

1.1.2. Improved function following suppression of IEDs

Treatment that suppresses IEDs has been associated with cognitive and behavioral improvements in children, similar to what occurs with the natural resolution of nocturnal IEDs as described above. Pressler et al. [32] demonstrated that global ratings of behavior improved in children with epilepsy who experienced decreased frequency or duration of IEDs. Several case studies have reported improved cognition and behavioral functioning in both adults and children in whom IEDs were better controlled [11,33]. These findings suggest that behavioral and cognitive problems were exacerbated by IEDs.

1.1.3. Language reorganization related to IEDs

Language reorganization correlates with the presence of left interictal spikes [34]. Recent work suggests that epileptiform discharges experienced in children with BCECTS lead to the reorganization of language functions [29], with some evidence that only frontal lobe language regions (e.g., Broca's area) reorganize, resulting in mixed language dominance [28,35].

1.2. Animal research related to the effects of interictal epileptiform discharges on cognition and behavior

Several studies in animals highlight a similar relationship between the occurrence of interictal spikes and behavioral function [36]. For example, Holmes and colleagues [37] demonstrated that hippocampal spikes occurring during a memory retrieval phase of processing disrupted the performance of rats on a delayed match-to-sample task. In contrast, similar spikes occurring during the encoding or maintenance phase of learning did not appear to have an appreciable effect. They also reported that the response time of the animals was much slower when such spikes occurred during performance. These researchers have also extended their work into a paradigm with humans, demonstrating that hippocampal spikes could disrupt memory performance when occurring during either retrieval or maintenance of learned information [6]. Interictal spikes that were bitemporal or arose from the TL region contralateral to seizure onset were most disruptive. This work again highlights that it may be critical to examine highly specific functions mediated by neural regions where the IEDs occur. That is, spikes from other brain regions were not associated with task failure, and thusly, overall effects may have been missed if IEDs had been treated as homogenous phenomena. Moreover, it suggests that it may be equally important to tie subcomponents of broader processes (e.g., retrieval and encoding phases of memory) to the temporal occurrence of epileptiform activity.

Animal studies also demonstrate that interictal spikes occurring during certain developmental windows may be more likely to have a cumulative negative effect on cognition. For example, rabbits with interictal spikes induced during early development were shown to have an abnormal distribution of receptive field types in certain brain regions (e.g., lateral geniculate nucleus) ipsilateral to their occurrence [38]. In another study, rat pups experiencing interictal spikes after being given a low dose of flurothyl during early development showed significant spatial memory deficits as adults, compared with age-matched controls [39]. This impairment appeared to be due to impairment of cell formation in the hippocampus. These findings raise the possibility that IEDs during early human development could have profound effects on later cognitive and behavioral function [40].

1.3. Negative results for the effects of interictal epileptiform discharges on cognition

Dodrill reported that seizure-related variables, including IEDs, predicted only a minimal amount of variance in a battery of neurocognitive measures and concluded that such factors had minimal effect on cognitive testing [41]. However, this paper made an attempt to relate spike counts to cognitive data in a broad manner without examining combinations of spike type and location with different types of cognitive ability. In a more recent study, Dodrill and Ojemann argued that even recent seizures do not appreciably affect cognitive performance once the patient is no longer clinically postictal [42]. However, in the latter study, the occurrence of a seizure during the last 24 h was based upon patient and family member self-report and not objective electrophysiological data.

1.4. Overview of case presentations

The first clinical case provides evidence that subclinical IEDs occurring frequently over the course of a day of neurocognitive testing can result in