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Interictal Epileptiform Discharge Effects on Neuropsychological Assessment and Epilepsy Surgical Planning

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Abstract

Both animal and human research suggests 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 the effects of IEDs may be substantial and informative for surgical planning. In the first case, we present an epilepsy patient 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

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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).

Keywords

interictal epileptiform discharges; surgical outcome; neuropsychological assessment

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 post-surgical neuropsychological change.

1.1. Research Demonstrating the Effects of Interictal Epileptiform Discharges on Cognition and Behavior

While research examining the effect 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 epilepsy patients experiencing IEDs during as little as 1% of the cognitive assessment period, performed significantly slower on tasks [10]. A 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 visuo-spatial/visuo-motor 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 epilepsy patients 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.

1.2. Indirect Evidence For the Affect of IEDs on Cognition and Behavior

1.2.1. 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 most 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 to 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].

1.2.2. Improved Function Following Suppression of IEDs

Treatment that suppresses IEDs has been associated with cognitive and behavioral improvement 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.

1.2.3. 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 leads to 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].

1.3. 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 either during 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 to 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].

1.4. 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 affect 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 post-ictal [42]. However, in the latter study, the occurrence of a seizure during the last 24 hours was based upon patient and family member self-report and not objective electrophysiological data.

1.5. 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 a performance pattern of severe focal dysfunction, consistent with the location of the IEDs, but not observed with testing on a separate occasion. The second case demonstrates that cognitive performance can vary widely when IEDs occur, often leading to contradictory or inconsistent results that would create problems for interpretation in the absence of simultaneous EEG data. In both cases, the observed pattern of dysfunction was one to two standard deviations below the patients' more adequate cognitive performance, and could have resulted in errors in surgical planning. While the data in the first case was useful for confirming seizure localization, one would have concluded that the patient was at low risk of cognitive decline with surgery, if these data had been mistakenly assumed to represent his baseline. In both cases, abnormal performance validity measures could have been mistaken for poor motivation for testing on the part of the patient (e.g., inadequate effort), but instead accurately reflected the suboptimal nature of functioning resulting from frequent, focal epileptiform activity.

Methods

2.1. Subject 1

The patient was a 42 year-old, right-handed, married, Caucasian male who underwent neuropsychological evaluation while undergoing video-EEG monitoring for possible epilepsy surgery. He experienced measles encephalitis at the age of 5 years, and developed complex partial seizures at 14 years. Seizures were characterized by unresponsiveness and lip smacking without motor involvement, loss of bowel or bladder control, or tongue biting. He experienced clusters of seizures every one to three months, and his family's report of "memory lapses" raised the possibility that the current IED phenomenon might have been occurring fairly frequently as well. Rare secondary generalization occurred in the context of medical noncompliance or subtherapeutic antiepileptic drug levels. This patient had no history of birth injury, developmental delay, febrile seizures, psychiatric comorbidities, or head trauma. Anti-epilepsy drug regimen included sodium divalproex (1250 mg TID), gabapentin (600 mg TID), and mephobarbital (200 mg BID), and was stable across all neurocognitive evaluations. The patient had an Associate's degree and was employed as a telephone technician for 15 years.

2.2. Procedures

2.2.1. Relevant Medical Procedures—3T MRI of the brain revealed left mesial temporal sclerosis (MTS) and mild, diffuse volume loss. During his EMU admission, interictal epileptiform activity was abundant, consisting of left anterior TL spikes, which were observed in all states, but most frequently during drowsiness and stage 2 sleep. The patient underwent neuropsychological assessment on the first full day of his admission, and left anterior TL spikes occurred frequently throughout the entire day of testing (more than 50% of the time). Following his testing, the patient experienced four electrographic seizures, which were associated with either left anterior temporal or occasionally bitemporal discharges. The bitemporal pattern was observed late into the patient's seizures, well after clinical onset, and was not believed to indicate independent seizure origin from the contralateral side. All events were characterized by unresponsiveness, lip smacking, fumbling with clothing, and post-ictal dysphasia. Prior outpatient EEG results had been read as normal and free from IEDs during those recording periods. Results of the Wada procedure revealed that the patient was left hemisphere dominant for speech, and that his contralateral temporal lobe was able to adequately support memory function.

2.2.2. Neuropsychological Findings—Initial neuropsychological testing was performed during inpatient epilepsy monitoring unit (EMU) evaluation at the University of Washington Regional Epilepsy Center, and follow-up testing was completed on an outpatient basis when he returned for Wada evaluation. As seen in Table 1, during his EMU admission, the patient exhibited a pattern of performance suggesting left fronto-temporal lobe dysfunction, including severely impaired performances on most tasks of auditory/verbal learning and memory and visual confrontational naming ability despite average to high average visual memory performance. Mild deficits involving aspects of executive functioning, including problems with generative fluency, response inhibition, and mental flexibility were also noted. Semantic fluency (impaired) was much worse than phonemic fluency (low average), a pattern suggesting primarily TL dysfunction [43].

The patient exhibited many scores that were average or better on tasks involving visual memory, general intellectual functioning, remaining executive skills, and most aspects of language processing. The results suggested dominant TL dysfunction, with possible disruption of frontal lobe regions presumably reflecting dysfunction of the broader temporo-frontal lobe networks secondary to ongoing seizures. Results also demonstrate that IED effects on function can be circumscribed rather than a widespread disruption. The patient did not exhibit any significant emotional distress during clinical interview or on formal measures of mood, although he did report some mild anxiety and concern over the effect of ongoing seizures and what he viewed as transient disruptions in his ability to function at work and at home.

The patient also failed performance validity testing. Performance validity tests (PVTs) are typically used to characterize task engagement and effort, but these measures may also be failed in the context of significant generalized cognitive impairment. Thus, validity testing suggested that he was either severely amnestic, which was inconsistent with his clinical presentation and excellent work history, or alternatively, some unknown variable was affecting his profile.

During epilepsy surgical planning conference, the attending epileptologist reported that abundant t left TL IEDs occurred throughout the entire neuropsychological evaluation. This record is no longer available for re-review, so we cannot be more precise regarding spike count. The presence of frequent IEDs during evaluation, and the failed performance validity testing suggested that the neuropsychological test findings might not be valid measures of true ability levels, and repeated neuropsychological testing was scheduled to be performed when he returned for Wada testing. We used alternate measures where available to avoid practice effects.

Follow-up testing was performed approximately 6 weeks later. Significant performance improvements across multiple measures were observed and were more in keeping with the patient's level of daily functioning. Although mild deficits in auditory/verbal learning and naming ability were observed during the second evaluation, performance was better than the severely impaired levels initially observed. Mild gains on some of the attentional measures and overall IQ scores were also noted.

2.2.3. Surgical Recommendations—Because Wada results confirmed left hemispheric language lateralization and demonstrated right cerebral capability of encoding new information, a left anterior temporal lobectomy was recommended. Based on the constellation of findings from the second evaluation in which there was only mild verbal learning and naming difficulty, we predicted that the patient would be at risk for further auditory/verbal memory decline with surgery. Seizure onset occurred during his teen years, and there was no indication of any brain reorganization based on available preoperative data. In addition, the mild naming and verbal memory deficits were exacerbated during IEDs suggesting that they were still mediated by this region. The presence of left MTS suggested, however, that there was only mild risk for postoperative verbal memory decline, although we suspected a high risk of naming decline with an open resection procedure [44].

The patient underwent a tailored anterior TL resection with cortical stimulation language mapping. He was seizure free at one-year follow-up evaluation (Engel Class I outcome). Nevertheless, he experienced significant restrictions in naming ability and his already compromised verbal fluency skills, and also declined on verbal memory measures. While he did not return for neuropsychological assessment with our laboratory, he was evaluated and treated by the rehabilitation program at UW. He was referred to this program when unable to return to work following surgery, and was continuing to receive outpatient services 6 months into his recovery. He eventually showed some improvement in memory but permanent compromise of select language functions as predicted, and required adjustments in his vocational routine in order to return to work. Raw scores were not available to us, but naming measures reportedly remained more than 2 standard deviations below the patient's optimal baseline performance.

3.1. Subject 2

This patient was a right-handed, right-footed, Caucasian male in his late 20s who had developed new onset seizures of unknown cause less than 2 years earlier. He had a college degree and was gainfully employed in a professional setting. Medical history was unremarkable, and there was no family history of seizures. The patient experienced complex partial seizures (CPS) that resulted in brief lapses in responsiveness, difficulty understanding others, and difficulty speaking. Initially, the patient would stand up during his seizures and point. However, this motor manifestation stopped after initiation of AED treatment. At the time of the current evaluation, the patient was experiencing several events per month (20 or more). He also had a history of experiencing at least two events involving secondary generalization since seizure onset. He reported a history of mild depression and alcohol abuse that preceded the onset of seizures. He had received counseling for his substance use issues and for anger management. The patient's AED regimen included levetiracetam (4000 QD) and oxcarbazepine (300 mg BID). The patient was being considered for epilepsy surgery intervention when evaluated by our service.

3.2. Procedures

3.2.1. Relevant Medical Procedures—Video-EEG monitoring captured three of this patient's characteristic spells. During two events he exhibited expressive speech difficulties, while he exhibited receptive language problems during the third. All three events were associated with rhythmic theta activity over the left anterior TL region, which evolved in morphology and frequency, consistent with electrographic seizures. Interictally, the patient experienced occasional left temporal sharp wave activity (F7, T3) seen throughout the recording. Findings were consistent with focal epilepsy of left TL onset. 3T MRI of the brain was notable for left MTS. FDG PET-CT was notable for decreased uptake in the left lateral and mesial TL regions.

3.2.2. Neuropsychological Findings—Neuropsychological evaluation was completed on an outpatient basis at Emory University Hospital while the patient was simultaneously undergoing an ambulatory EEG recording. Results of this evaluation are included in Table 2. The patient was noted to experience occasional left TL interictal discharges during the morning of his evaluation (spikes occurred infrequently, with just a few spikes per minute), as well as a brief run of interictal theta activity (lasting for 1–2 minutes in duration). At one point, during the morning session, the patient reported that he felt funny, although he never became unresponsive or confused. Neither our staff nor the patient noted any overt clinical seizure activity. He reported that his last clinical event had been several days earlier.

During the morning session, when the patient exhibited interictal epileptiform activity, he failed a performance validity test that essentially involved recognition recall of word pairs, and also exhibited a severely impaired list learning performance. In contrast, during the afternoon, when not experiencing epileptiform activity, the patient performed normally on a harder word-pair learning task than he had failed during the morning. He also exhibited a normal contextual learning performance. Visual memory was decreased during the morning as well, but less so during the afternoon. Otherwise, the patient displayed high average general intellectual functioning, with an advantage on tasks related to verbal abilities (high average) versus those dependent on nonverbal, perceptual skills (average). Language skills were very strong, with no significant indication of any dysfunction in this area. Average or better performances were observed for visuo-perception and visual-spatial processing, constructional ability, gross motor speed, and executive functions. The patient's mood appeared mildly depressed on self-report inventories. His personality style appeared to be similar to persons characterized as reckless, impulsive, and angry.

An initial report from the attending epileptologist suggested that the patient's ambulatory EEG had been normal, although this reading was later revised as indicated above to include the presence of interictal epileptiform activity during the morning session of testing. Prior to receiving this update, we began to think that the inconsistent memory patterns, which included failure on a performance validity test, must reflect poor task engagement. This interpretation was seemingly bolstered by the patient’s personality traits of anger, impulsivity, and noncompliance. However, the revised EEG interpretation demonstrated that the patient performed poorly on memory measures only when he had been experiencing epileptiform activity. Having this EEG data allowed us to avoid a very misleading, and potentially damaging conclusion. This patient is considered a generally good surgical candidate, but has not opted to undergo surgery at this time.

Discussion

Our review of the extant research literature on the possible relationship between IEDs and cognition makes a compelling case that IEDs are having a significant effect on behavior that is frequently unrecognized. Increasingly, more researchers are coming to this conclusion [40], yet clinical lore has long suggested that any effect is trivial and likely not worth considering. In this context, we believe that our current case examples, while not definitive proof of this concept, provide impetus for further study. We demonstrate that interictal epileptiform activity can seemingly affect neurocognitive results in an appreciable manner. We also show that the effects of IEDs on cognitive testing can be useful for confirming the lateralization and localization of seizure onset, although they often produce an inaccurate estimate of adequate baseline functioning that must be appreciated for optimal surgical planning. In both of our cases, our patients’ neurocognitive profiles suggested severe disruption of language dominant TL functions when IEDs were present in this region, yet such deficits were minimal in their absence. Without simultaneous EEG recordings, the relationship between IEDs and cognitive performance would not have been appreciated, and this may have hindered surgical planning for both patients. In the first case, we would have assumed that this patient’s memory and language functions were severely compromised, and may have underestimated potential risks of a surgical resection involving the dominant TL region. Instead, we were able to provide a more thorough assessment of the risks associated with surgery to the neurosurgeon and to the patient and his family, and take steps to protect intact areas of function (e.g., cortical stimulation mapping of language functions prior to open resection). In the second case, we were about to conclude that the patient was making only a suboptimal effort to participate in testing prior to our learning about the concurrent IEDs. Currently, with increasing alternative surgical interventions, such as responsive neurostimulation or stereotactic laser amygdalohippocampotomy (SLAH), accurate patient characterization with neurocognitive testing has increasing relevance for surgical planning [45, 46]. The first patient would currently be offered SLAH as a first line treatment option, as it is less likely to affect naming ability in such cases.

Growing evidence suggests IEDs can affect cognitive performance [4, 5], and this knowledge is of critical importance to those assessing cognition in epilepsy. Our cases indicate that even a gross knowledge of presence or absence of IEDs can be helpful in understanding cognitive performance.One limitation of this study involved our inability to re-review EEG data due to the retrospective, clinical nature of the cases. However, in the future, it may be possible to determine more specific relationships between cognitive function and the location, duration (e.g., number of spikes per minute), and type of discharges (e.g., frequency bandwidth), which would allow us to more accurately establish baseline function while perhaps contributing more useful data to the localization of seizure onset. More recently, it has been suggested that underlying electrophysiological rhythms, such as slow wave activity, may play an important role in cognition that goes beyond spike counting [47, 48].

If transient disruption of performance of the magnitude seen in our cases occurs in even a minority of our patients, it would be problematic for standard clinical assessment as currently practiced. In those epilepsy programs that assess epilepsy patients on an outpatient basis without EEG, such transient disruptions due to IEDs could not be detected. This could lead to erroneous decisions related to surgery and other treatments, and placement decisions related to school and disability. Likewise, the current study suggests that aspects of performance validity testing can be affected by epileptiform discharges, which could erroneously cast dispersions on the patient's motivation and compliance with testing. One might assume that they were not trying their best to perform accurately, when instead it would appear that the capacity for task engagement was actually compromised by unrecognized IEDs. The particular PVT failed by both patients in this study, the Word Memory Test (oral version), appears to be disrupted by recent or simultaneous TL spikes involving the language dominant hemisphere, but not be spikes occurring elsewhere in the brain [49–51]. Therefore, we err on the side of caution (i.e., assuming there may be an interaction of IED activity and poor memory performance in a given patient) when we observe this pattern of failure on this specific PVT and the presence of active dominant TL spikes. PVT measures were originally employed to make sure that patients undergoing neuropsychological evaluation were putting forth an accurate level of effort, as individuals can be less motivated to appear well in some contexts (e.g., legal decisions) or experience poor motivation for undergoing testing (e.g., a child being forced to undergo testing by a parent) [52]. They tend to be very easy tasks, which are often designed to look more difficult on the surface. Of note, failure on this PVT in the context of active IEDs should not be considered a false positive error of the performance validity test, as it has actually done its job of noting that testing is suboptimal. Instead, it is a true positive for poor task engagement, which is thought to have resulted from a transient physiological abnormality rather than a motivational issue.

An underestimation of a patient's baseline performance can affect the neurosurgeon's approach to their case, as they could assume that an impaired cognitive performance means that the patient has much less to lose secondary to surgery. As new minimally invasive therapies are available (e.g., stereotactic laser ablation, neurostimulation devices), accurate knowledge of baseline cognitive function should help to inform the decision making process for both the patient and neurosurgeon. Likewise, an underestimation of baseline performance could also lead to erroneous conclusions in outcome studies, or research using neurocognitive scores as an endpoint (e.g., we might falsely determine that there was no decline or even an improvement following surgery, when instead the patient may have actually gotten worse).

In our first case, there was an interesting dissociation that occurred between the contextual memory test (i.e., story recall) and the list learning and associative learning tasks, as the former did not appear to be affected by the subclinical epileptiform activity. This finding is an example of the dissociation that frequently occurs between tests of memory, and is supportive of the position that the latter tasks are more dependent on mesial TL structures [53]. Efforts to integrate cognitive performance in real-time with electrophysiology and neuroimaging assessments of functional connectivity have the potential to provide significant gains in understanding the neural networks underpinning multiple cognitive processes.

The magnitude of transient deficit observed in our case series is also worth noting. In case 1, the patient was generally amnestic throughout the day of testing during which he experienced frequent IEDs. This is consistent with the reports of the patient and his family that he had been experiencing increasing “memory lapses” that were troubling to his social and vocational functioning. We would presume that these complaints likely reflected days during which the patient experienced frequent IEDs. However, future prospective studies are necessary to establish that such relationships exist between cognitive function and the presence of IEDs.

A limitation of this report is the absence of simultaneous EEG during the second assessment of our first patient, so we cannot definitively state that interictal discharges were absent during this evaluation. However, the effects of IEDs appear more definitive in case number 2. Additionally, we have previously shown that interictal epileptiform activity occurring in the anterior TL region of the language dominant cerebral hemisphere is strongly associated with failure on the employed PVT measure [50, 51]. Therefore, we feel confident that even in the case of patient 1, his initial testing was related to this electrophysiological phenomenon, as he exhibited both this characteristic PVT pattern of performance and the presence of dominant TL IEDs during the initial inpatient video-EEG monitoring assessment. However, he easily passed the same and similar PVT and genuine memory measures on follow-up assessment. This phenomenon also appears consistent with family reports of occasional lapses in memory observed during recent years interspersed by normal function. The patient’s baseline EEGs had been normal prior to his EMU stay, suggesting that he experiences periods free from IEDs. Finally, there were no other significant differences between test occasions (e.g., medications regimen, psychiatric status, and general health were the same across assessments). This patient had a normal baseline EEG recording for the 24-hours prior to the first day of testing, and had not experienced a clinical seizure in more than one week, so it appears unlikely that the initial decrements had been related to any unrecognized seizure.

We believe that it important to obtain simultaneous EEG recordings during cognitive assessment in order to definitively resolve these issues, and we strive to get simultaneous EEG during pre-surgical neuropsychological evaluation performed in our outpatient clinic. Use of simultaneous EEG with neuropsychological testing in clinical practice has been suggested by others [54]. Having simultaneous EEG data is an advantage for completing presurgical cognitive testing in the monitoring unit. However, inpatient evaluations often involve changes in medication regimen, sleep deprivation, and a less controlled testing environment, as the goal of monitoring is to elicit seizure activity. We hope that greater use of simultaneous EEG will not only help clarify the frequency and magnitude of IED effects on neuropsychological evaluation, but will also permit a truer characterization of post-surgical neuropsychological change.

Consideration of the possible effects of IEDs on cognitive function is generally underappreciated by the epilepsy surgery community and rarely considered in the context of neuropsychological assessment. Despite emerging data suggesting its potential affect on real-world performance [6, 16], much clinical lore suggests that IEDs do not affect behavioral or cognitive function, with some clinicians maintaining that any relevant effects can be determined by an expert observer. Nevertheless, this review and case series demonstrates that epileptiform activity can be completely unsuspected by patients and their physicians alike. Our patients produced many scores one to two standard deviations below what appears to have been their actual ability. Group level studies not finding a relationship between IED occurrence and cognitive function likely miss this connection by failing to relate specific types of discharges to the specific cognitive functions associated with affected neural substrates. That is, such research paradigms tend to relate general, unspecified IEDs (i.e., differing types of abnormalities affecting differing brain regions) to broad cognitive functions without regard to known structure-function relationships, thereby decreasing the chance of finding highly specific, focal patterns.

While we do not believe the current case studies definitively establish the potential effects of IEDs on cognition, we believe that they raise strong suspicions about this possibility. Having simultaneous EEG during cognitive testing represents a clear-cut advance over earlier papers that attempted to draw correlations between data obtained on different occasions. We hope this review and case reports will generate additional interest in this area, as substantial funding will be needed to explore these issues in the rigorous manner that is required to establish these important relationships. Ultimately, simultaneous EEG will be required in larger samples of epilepsy patients with greater lead-time to establish baseline performance during periods of normal electrographic periods and to re-test patients during and following IED occurrence to determine the pattern of effects and the time-course of their resolution.

Overall, recognizing when latent variables are disrupting cognitive performance is critical in the epilepsy surgery arena, as failure to do so can lead to major erroneous decisions in surgical planning and life decisions. Future research should endeavor to determine the typical frequency of occurrence of IEDs during neuropsychological evaluation, and determine relationships between electrophysiological characteristics of IEDs and cognitive performance and functional behavior. Additionally, our cases highlight the possibility that testing a patient when unilateral IEDs or even a seizure are occurring may be diagnostically useful for confirming the lateralization or localization of seizure onset.

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Highlights

- We review extensive animal and human research suggesting interictal epileptiform discharges (IEDs) may affect cognition.
- Case series data demonstrate memory impairment and cognitive dysfunction is associated with the presence of IEDs using simultaneous EEG during testing.
- The occurrence of IEDs can lead to spurious conclusions about neurocognitive data, and can misinform epilepsy surgical planning, outcome research, and prediction of individual risk associated with surgery.
- Understanding the relationship between IEDs and cognition can improve seizure onset classification with neuropsychological testing and can illuminate underlying brain-behavior relationships.

Table 1

Select Results of Neurocognitive Testing During Video-EEG Monitoring and Six Weeks Later at Time of Wada Procedure for Patient 1.

Tests Administered	Results During video-EEG Stay	Results on Day of Wada
General IQ*	WAIS-III FSIQ = 99, VIQ = 104, PIQ = 91	WASI FSIQ = 108, VIQ = 110, PIQ = 102
Performance Validity Testing*	Failed 3/3 effort measures from the Word Memory Test (oral version), but produced a genuine impairment profile	
Boston Naming Test*	Raw = 39/60, impaired	Raw = 48/60, mildly impaired
Semantic Fluency (animals)**	Raw = 9, Z= −3.0, <1st %ile	Raw = 14, Z= −1.70, 4th %ile
Letter Fluency (COWA)	Raw = 18, Z= −2.0, 2nd %ile	Raw = 24, Z= −1.70 4th %ile
Complex List Learning	Rey Auditory Verbal Learning Test	Verbal Selective Reminding Test (Form 1)
	Trial 1 = 6/15,Z= −0.56, 28th %ile	
	Trial 5 = 9/15,Z= −2.17, 1st %ile	
	5-Trial Total = 40/75, Z= −2.21, 1st %ile	LTS = 108,Z= −0.25, 44th %ile
	Immediate = 6/15, Z= −2.39, 1st %ile	CLTR = 74, Z= −0.70, 23rd %ile
	Delayed = 0/15, Z= −4.52, <1st %ile	Delayed = 11/12, Z= 0.22, 51st %ile
	Recognition = 9/15, Z= −8.45, <1st %ile	Recognition = 12/12, Z= 0.0, Normal
WMS-IV Logical Memory		
Immediate Recall:	Raw = 41, 50th %ile	N/A
Delayed Recall:	Raw = 17, 25th %ile	
Verbal Paired Associates**	WMS-III	WMS-I
Immediate:	Raw = 2, Z= −3.0, 1st %ile	Raw = 16, Z= −0.75, 21st %ile
Delayed:	Raw = 0, Z= −4.0, <1st %ile	Raw = 9, Z= −1.27, 12th %ile
Face Recall	WMS-III Faces	N/A
Immediate:	Raw = 34, 25th %ile	
Delayed:	Raw = 40, 75th %ile	
Recall of Designs	WMS-III Visual Reproduction	N/A
Immediate:	Raw = 76, 16th %ile	
Delayed:	Raw = 77, 75th %ile	
Recognition:	Raw = 44, 50th %ile	
Trailmaking Test**	Part A = 29 seconds, Z= −0.7, 23rd %ile	Part A = 26 seconds, Z= −0.33, 37th %ile
	Part B = 129 seconds, Z=−4.0, 1st %ile	Part B = 68 seconds, Z= −0.53, 30th %ile
Finger Tapping Test		
Dominant hand:	Raw = 49, 21st percentile	Raw = 54, 50th percentile

Tests Administered	Results During video-EEG Stay	Results on Day of Wada
Nondominant hand:	Raw = 46, 30^{th} percentile	Raw = 48, 45^{th} percentile
Grip Strength		
Dominant hand:	Raw = 45, Z= −0.96, 18^{th} %ile	Raw = 45, Z= −0.96, 18^{th} %ile
Nondominant Hand:	Raw = 43, Z= −0.96, 18^{th} %ile	Raw = 43, Z= −0.96, 18^{th} %ile
Category Test	13 Errors, normal	N/A

Note. IQ = intellectual quotient, WAIS-III = Wechsler Adult Intelligence Scale (3^{rd} edition), FSIQ = Full Scale IQ, VIQ = Verbal IQ, PIQ = Performance IQ, WASI = Wechsler Abbreviated Scale of Intelligence, COWA = Controlled Oral Word Association Test, LTS = Long Term Storage, CLTR = Continuous Long-Term Retrieval, WMS-III = Wechsler Memory Scale (3^{rd} edition), WMS-I = Wechsler Memory Scale. The patient performed significantly better on tests marked with an asterisk when assessed at a second time point presumably free of IEDs. One asterisk indicates that the comparison was based on reliable change scores while two asterisks indicates that the comparison represented at least a 1 standard deviation change in performance.

Table 2

Select Results of Neurocognitive Testing During Neuropsychological Assessment with Simultaneous EEG Recordings for Patient 2.

Tests Administered	Test Scores	EEG Status at Time of Specific Test
General IQ	WAIS-IV FSIQ = 110, VCI = 114, PRI = 105	Some subtests administered during epileptiform discharges, and others during afternoon when IEDs were absent
Performance Validity Testing	Failed 1/3 effort measures from the Word Memory Test (oral version), and produced a genuine impairment profile	Epileptiform activity present immediately prior to test performance (occasional TL spikes)
Boston Naming Test	Raw = 56/60, WNL	This test was completed during the afternoon after epileptiform activity had ceased for more than 2 hours.
Complex List Learning	Rey Auditory Verbal Learning Test Trial 1 = 6/15,Z= −1.53, 6th %ile Trial 5 = 6/15,Z= −3.0, 1st %ile 5-Trial Total = 27/75, Z= −3.0, 1st %ile Immediate = 0/15, Z= −4.0, <1st %ile Delayed = 2/15, Z= −3.0, 1st %ile Recognition = 3/15, Z= −4.0, <1st %ile	Epileptiform activity present immediately prior to and during test performance (theta activity)
WMS-IV Logical Memory Immediate Recall: Delayed Recall:	 Raw = 41, SS = 10, 50th %ile Raw = 22, SS = 9, 37th %ile Recognition = 23/30, low average	This test was completed during the afternoon after epileptiform activity had ceased for more than 2 hours.
WMS Verbal Paired Associates Immediate: Delayed:	 Raw = 20; Z= −0.50; 30th %ile Raw = 8; Z= 0.54; 70th %ile	This test was completed during the afternoon after epileptiform activity had ceased for more than 2 hours.
WMS-III Visual Reproduction Immediate: Delayed: Recognition:	 Raw = 13, 95th %ile Raw = 2, 1st %ile Raw = 3/4, Low Average	This test was completed during the morning, shortly after IEDs were present.
Rey Complex Figure Test Copy Task: Immediate Recall: Delayed Recall:	 Raw = 36/36, Average Raw = 20.5, 21st %ile Raw = 16.5, 4th %ile	This test was completed during the afternoon after epileptiform activity had ceased for more than 2 hours.

Note. IQ = intellectual quotient, WAIS-IV = Wechsler Adult Intelligence Scale (4th edition), FSIQ = Full Scale IQ, VCI = Verbal Comprehension Index, PRI = Perceptual Reasoning Index, IEDs = Interictal Epileptiform Discharges, WMS-IV = Wechsler Memory Scale (4th edition), WMS = Wechsler Memory Scale.