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Review

The new approach to classification of focal epilepsies: Epileptic discharge and disconnectivity in relation to cognition

Vera Dinkelacker [a,b,*], Sophie Dupont [b,c], Séverine Samson [c,d]

[a] Neurology Unit, Rothschild Foundation, 25 Rue Manin, 75019, Paris, France
[b] Centre de Recherche de l'Institut du Cerveau et de la Moëlle Épinière (CRICM), UPMC-UMR 7225 CNRS-UMRS 975 INSERM, Paris, France
[c] Epilepsy Unit, Pitié-Salpêtrière Hospital, 47–83 boulevard de l'Hôpital, 75013, Paris, France
[d] Laboratoire PSITEC (EA 4072), Université de Lille 3, France

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ABSTRACT

The new classification of epilepsy stratifies the disease into an acute level, based on seizures, and an overarching chronic level of epileptic syndromes (Berg et al., 2010). In this new approach, seizures are considered either to originate and evolve in unilateral networks or to rapidly encompass both hemispheres. This concept extends the former vision of focal and generalized epilepsies to a genuine pathology of underlying networks. These key aspects of the new classification can be linked to the concept of cognitive curtailing in focal epilepsy. The present review will discuss the conceptual implications for acute and chronic cognitive deficits with special emphasis on transient and structural disconnectivity. Acute transient disruption of brain function is the hallmark of focal seizures. Beyond seizures, however, interictal epileptic discharges (IEDs) are increasingly recognized to interfere with physiological brain circuitry. Both concomitant EEG and high-precision neuropsychological testing are necessary to detect these subtle effects, which may concern task-specific or default-mode networks. More recent data suggest that longstanding IEDs may affect brain maturation and eventually be considered as a biomarker of pathological wiring. This brings us to the overarching level of chronic cognitive and behavioral comorbidity. We will discuss alterations in structural connectivity measured with diffusion-weighted imaging and tractography. Among focal epilepsies, much of our current insights are derived from temporal lobe epilepsy and its impact on neuropsychological and psychiatric functioning. Structural disconnectivity is maximal in the temporal lobe but also concerns widespread language circuitry. Eventually, pathological wiring may contribute to the clinical picture of cognitive dysfunction. We conclude with the extrapolation of these concepts to current research topics and to the necessity of establishing individual patient profiles of network pathology with EEG, high-precision neuropsychological testing, and state-of-the-art neuroimaging.

This article is part of a Special Issue entitled "The new approach to classification: Rethinking cognition and behavior in epilepsy".

1. Introduction

The new classification of epilepsy intends to set an entirely revised framework that allows flexible adaptation to major advances in clinical and fundamental neuroscience [1]. This framework spans modifications of classical terminology and definitions and challenges the notion of 'expert opinion' as the major defining factor. Emphasis is given to the phenomenological description of the epilepsies in order to facilitate the integration of new concepts and discoveries. As previously emphasized by Wilson and Baxendale [2], this new classification has significant implications for the way we conceptualize and assess cognition and behavior in epilepsy.

Within this new classification approach, clinical evidence is divided into two distinct levels: a first basic level, employing the classical categorization based on seizures (generalized or focal) and their semiology; and a second, overarching level based on epileptic syndromes and underlying causes. The latter approach questions many former concepts, and to a certain degree, even the strict distinction of generalized and focal epilepsies, while underlining the importance of origins (genetic, structural/metabolic, and unknown) and the age at disease onset. Ultimately, the new classification clearly embraces the concept of network disease, both for focal and for generalized epilepsies. Note that within the context of the present paper, special emphasis will be given to the focal epilepsies and particularly temporal lobe epilepsy as this constellation is particularly well examined, both for acute and for chronic cognitive curtailing. Cognitive deficits associated with epilepsy may range from subtle impairments in material-specific tasks and/or

* Corresponding author at: Rothschild Foundation, 25 Rue Manin, 75019 Paris, France.
E-mail address: v.dinkelacker@gmail.com (V. Dinkelacker).

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moderate reduction in IQ to significant intellectual disability. In this review, emphasis will be given to the former effects in the context of focal epilepsy.

With regard to cognition and behavior, signs and symptoms can be newly defined in both the acute and the chronic level of classification. On the first, short-lived level of seizures, the dyscognitive features, their acute and postictal evolution are at the center of the phenomenological approach [1]. Cognition, rather than loss of consciousness, thus has a major contribution to the definition of acute events and their diagnostic value [2]. Here, it is also worth keeping in mind that epileptic discharges occur on a continuum. Interictal and subclinical discharges also have the potential to disrupt neuropsychological performance and thus constitute an additional factor in the phenomenological approach [3,4].

On the second, overarching level, curtailing of cognition is a landmark of chronic epilepsy and can yield fundamental insights into network disease [5]. Using precise cognitive screening tools and state-of-the-art neuroimaging will be the mainstay of future research on this topic [2]. As a matter of fact, functional and structural neuroimaging techniques convey a complex picture of disconnectivity and pathological wiring, most notably in focal epilepsies [6]. This new approach of focal epilepsies and their relation to ipsi and contralateral hemispheric networks [1] is increasingly evident in current research on structural connectivity. Furthermore, seizures and interictal epileptic discharges (IEDs) remain a major confound in the correlation of structural network disease and cognition and therefore need to be further examined.

This review intends to canvass cognition through the prism of both levels of the new classification. In the first section, we will review the evidence for acute network curtailing during IEDs. In the second section, we will consider the wealth of studies on structural disconnectivity and pathological wiring and its relation to cognition. On the imaging level, we will focus on structural connectivity since additional aspects of network pathology, such as functional connectivity and graph theoretical approaches, are treated in a complementary paper of this special issue. A large body of evidence will be examined in relation to alterations in brain networks and cognition. It seems likely, however, that many of these considerations also hold for behavioral aspects of chronic epilepsy, such as depression and anxiety. We will then conclude by discussing the relevance of brain connectivity for the exploration of cognitive phenotypes and the future perspectives of rendering a multimodal individual patient profile.

2. Acute disruption of cognitive networks by epileptic discharges

2.1. Acute impact of seizures and IEDs on cognition

The basis of the new classification remains centered on seizures and their semiology. With respect to cognition, it is worth noting that the distinction of simple partial and complex partial seizures has been formally abandoned [1], to favor a purely phenomenological approach. Semiology thus gains new impetus, and notably dyscognitive features are used to substitute categorization with regard to loss of consciousness [1].

It is beyond the scope of this review to detail all aspects of cognitive curtailing during a seizure. The reader is referred to the recent literature regarding transient deficits in higher order brain function and the networks implicated [7,8]. Note, however, that many authors underline the importance of the level of awareness and consciousness and feel that it should remain a paramount feature of seizure classification [9–11].

The basic level of the new classification only marginally considers IEDs, mainly as a tool to describe electroclinical syndromes. From the viewpoint of cognitive research, however, it is a crucial point that epileptic discharges lie on a continuum from interictal and short-lived subclinical discharges to clinically apparent seizures [3,12,13], with a variable degree of cognitive dysfunction.

2.2. Transient cognitive impairment concomitant to IEDs

While first discussed by Schwab (1939) [96] with respect to slowing of reaction times during absence seizures, the concept of "transient cognitive impairment" was proposed by Aarts and colleagues in 1984 [14] to designate functional deficits during subclinical spike or spike–wave discharges. It is a longstanding debate whether IEDs can be reliably distinguished from minor seizures [3,15]. Yet, recent evidence has lent strength to the concept of IEDs interfering with cognitive function [12,16].

IEDs have been shown to affect a broad range of cognitive functions, from attention and memory to sensorimotor tasks or executive functions, with a special impact on speed of information processing [17]. Detection of these transient deficits critically depends on the neuropsychological test delivered. According to Aldenkamp and colleagues, the test features with high sensitivity are visual input mode, longer testing duration, and high information processing demand [3].

2.3. IEDs disrupt specific and global brain circuitry

What do we know about the networks particularly affected by IEDs? Two hypotheses are advanced, which may be complementary: i) the disruption of specific cognitive networks by IEDs and ii) the disruption of the default-mode network, the latter causing an impairment of attention that may interact with specific cognitive functions.

Regarding the first hypothesis, recent evidence suggests that IEDs may disrupt specific cognitive networks. For instance, Kleen et al. [16] investigated memory performance in patients who underwent stereo-EEG for refractory temporal lobe epilepsy. Concomitant to the testing, IEDs in the hippocampus contralateral to the seizure focus were associated with retrieval impairment. Memory dysfunction was only observed for repetitive or spatially diffuse but not for single focal IEDs. The results are consistent with the hypothesis that IEDs interfere with specific networks supporting memory processing, which extend beyond the ipsilateral hippocampal region. These results emphasize the importance of brain network synchrony in supporting memory function [13]. Similarly, Chaudhary and colleagues [18] used simultaneous video-EEG and functional imaging to demonstrate that generalized IEDs altered the working memory-related hemodynamic responses in frontal-lobe networks. These findings thus confirm the impact of IEDs on task-specific brain circuitry.

In line with the second hypothesis, IEDs may interfere with underlying networks that respond to a wide spectrum of cognitive demand, which is the case with the default-mode network (DMN). The DMN is an ensemble of brain regions that is active at rest but reduces its activity during goal-directed behavior [19]. Notably, it comprises the posterior cingulate cortex, precuneus, and medial prefrontal and lateral parietal cortices. Fahoum et al. [20] studied six patients with epilepsy who underwent scalp EEG-fMRI and later stereotaxic intracerebral EEG (SEEG), sampling regions of the DMN. They found coherent DMN deactivation and SEEG frequency changes associated with IEDs. By affecting the DMN, IEDs may therefore momentarily reduce consciousness level and cognitive reserve.

2.4. IEDs as a biomarker of the underlying network disease

While it seems well acknowledged that seizures and IEDs affect cognition in an acute manner, we shall now consider IEDs in terms of electroclinical syndromes and long-term network disease. There is clear clinical evidence for an impact of IEDs on cognitive function in specific epileptic syndromes affecting children such as the syndrome of electrical status epilepticus during slow-wave sleep, Landau–Kleffner syndrome, and epileptic encephalopathies [21]. However, it appears reasonable to consider that the cognitive or behavioral deficits in the course of these syndromes are multifactorial, based on pathologic networks and not exclusively caused by IEDs [22].