



## Review

# Reprint of: The new approach to epilepsy classification: Cognition and behavior in adult epilepsy syndromes☆

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## ABSTRACT

The revised terminology and concepts for the organization of seizures and epilepsy proposed by the ILAE Commission on Classification and Terminology in 2010 allows for a number of new opportunities in the study of cognition and behavior in adults. This review examines the literature that has looked for behavioral and cognitive correlates of the newly recognized genetic epilepsies in adults. While some studies report clear cognitive phenotypes associated with specific genetic mutations in adults with epilepsy, others report remarkable clinical heterogeneity. In the second part of this review, we discuss some of the factors that may influence the findings in this literature. Cognitive function is the product of both genetic and environmental influences. Neuropsychological phenotypes under direct genetic influence may be wider and more subtle than specific deficits within discrete cognitive domains and may be reflected in broader, multidimensional measures of cognitive function than those tapped by scores on standardized tests of function. Future studies must be carefully designed to reflect these factors. It is also imperative that studies with negative findings are assigned as much value as those with positive results and published accordingly.

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## 1. Introduction

The revised terminology and concepts for the organization of seizures and epilepsy proposed by the ILAE Commission on Classification and Terminology (2005–2009) recommended a shift away from ‘the shadows of expert opinion and assertion-dominated arguments’ [1] to a classification that ‘fully reflects and profits from all of the other advances being made in basic and clinical neurosciences’, in order to ensure that these advances can be incorporated into clinical practice. While this is a laudable aim, the practicalities of devising a classification system that is flexible enough to meet these aims yet practical enough to be used and (crucially) accepted by the clinical community are manifold. In the spirited debate that followed the publication of the Commission report in the literature [2,3], it can be possible to lose

sight of the fact that the Commission authors emphasized that they had made no changes (other than to the nomenclature) to the list of epilepsy syndromes that had already been recognized and updated in the 2006 Task Force report [4]. However the 2005–2009 Commission recognized that the old idiopathic, symptomatic, and cryptogenic classifications were limited to some extent by the adequacy of the available data. All seizures are ‘symptomatic’ of something, but whether we can identify that ‘something’ depends to some extent on the available technology. The advent of MRI resulted in a large number of people with epilepsy ‘shifting’ their diagnoses from a cryptogenic or idiopathic epilepsy to a ‘symptomatic’ epilepsy.

The new classification retains the emphasis on the etiology of the seizure disorder but recognizes three underlying types of cause: 1. genetic, 2. structural/metabolic, and 3. unknown. People with structural/metabolic conditions may also have a genetic component to their condition, but there is a separate disorder interposed between the genetic defect and the epilepsy.

In addition to a revised classification of epilepsy based on the etiology of the condition, the Commission also revised the classification of seizures.

In the same way that etiology lies at the heart of the new classification of the epilepsies, the origin of a seizure, based on the neurophysiological

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characteristics of the ictal onset, remains at the heart of the new classification of seizures. Generalized seizures originate within a bilaterally distributed network, while focal seizures are characterized as those that originate within one hemisphere. However, generalized seizures can be asymmetric, and focal seizures can propagate to the contralateral hemisphere. The team noted that we currently have inadequate information to create a scientific classification within focal seizures but recommended that seizures be classified according to features that are the most useful for a given purpose. In addition to noting the important distinction between focal seizures that are associated with an impairment of consciousness (also called a dyscognitive focal seizure) and those that occur without impairment of consciousness or awareness, the Commission also recommended the use of the Glossary of Ictal Semiology [5] for well-defined descriptive terms.

This commentary examines the clinical and research implications of the revised terminology and concepts for clinicians and researchers concerned with cognitive and behavioral problems in adults with epilepsy.

## 2. Neuropsychological characteristics of genetic epilepsies in adults

The majority of neuropsychological studies in people with genetic epilepsy have been conducted in pediatric populations, reflecting the general predominance of genetic studies in children [6–9]. Studies that have looked for a common neuropsychological deficit in people with inherited gene mutations have had mixed results to date, with some reporting very specific relationships between neuropsychological function and genetic variables [10–12] and others finding very few clinical correlations [13].

The neuropsychological deficits that have been associated with specific genetic epilepsies can be general, for example effects on IQ [11] or very specific, such as the core deficit in cognitive flexibility that has been reported in people with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a nonlesional condition associated with a mutation of the gene coding for the alpha4 nicotinic acetylcholine receptor (nAChR) [12]. A more general deficit in IQ has been associated with different genetic profiles in people with tuberous sclerosis. The clinical picture in people with tuberous sclerosis is varied with a bimodal distribution of IQ and greater clinical and cognitive morbidity associated with tuber burden and epilepsy severity. van Eeghen et al. [11] found that TSC1 mutations were significantly associated with lower intellectual function, which was also the case for TSC2 protein-truncating and hamartin interaction domain mutations. However, other TSC2 mutations and small in-frame deletions were significantly associated with higher IQ's.

Passamonti et al. [13] examined the neuropsychological functions of thirteen patients, across three generations of a family who had a novel inherited splicing mutation of the SCN1A gene. There was very little homogeneity in the group, with half having no history of epilepsy, a normal EEG and cognitive profile, while the others had a wide variety of clinical symptoms including generalized epilepsy, Dravet syndrome, and focal epilepsy. Given the remarkable clinical heterogeneity in the group, it is unsurprising that this was mirrored by the neuropsychological findings.

These findings are in marked contrast to the results reported by Chowdhury et al. [10], who reported impaired cognitive function in people with epilepsy and their unaffected members. This is an interesting study to compare with the SCN1A study described above, as Chowdhury et al. did not utilize the new classification system but studied a group of patients with 'idiopathic generalized epilepsy' arguing that IGE has a strong genetic component. The new classification now states there must be 'a minimum threshold for presuming a form of epilepsy does, in fact, have a genetic basis. Undocumented assertions are not accepted' [1]. While a neuropsychological profile will not replace the genetic bedrock that allows the recognition of genetic epilepsies, the findings of Chowdhury et al. raise the intriguing possibility that neuropsychological studies may be helpful in directing this research. This possibility is also suggested by the findings of Valente et al. [14], who demonstrated

the existence of a subset of patients with JME with poorly controlled seizures who presented with broader impairments related to both cognitive deficits and impulsive traits. The authors argue that their findings indicate that patients with JME are not equally compromised by cognitive deficits, but rather that there are distinct groups of patients with JME.

Cognitive function is the product of both genetic and environmental influences. In people with epilepsy, antiepileptic medications, sleep disruption, and ictal, periictal, and interictal disturbance will all have a strong influence on function. These influences will vary. While an MRI will show a tumor regardless of how someone is feeling in the scanner or how much sleep they had the night before, both factors may have a very significant influence on their performance on a neuropsychological assessment. Of all of the standard clinical investigations in epilepsy, a neuropsychological assessment is the most prone to a type 1 error in the identification of an 'organic' deficit, when none exists. Given these biases, studies based on a one-off assessment (the vast majority) may not be sensitive enough to tease out subtle genetic influences from environmental factors. The neuropsychological phenotypes under direct genetic influence may be wider and more subtle than obvious deficits within specific cognitive domains, and could perhaps be reflected in broader measures of cognitive function such as change over time, or even more nebulous qualities such as variability in ability to function optimally, or diurnal fluctuations in function. Studies must be carefully designed to reflect these factors. It is also imperative that properly conducted studies with negative findings are assigned as much value as those with positive results and published accordingly.

## 3. Challenges of the revised terminology and concepts for the study of behavior and cognition in adults

Studies of cognition and behavior in people with epilepsy fall into two broad categories: those that treat people with epilepsy as a homogenous group and those that subdivide people with epilepsy according to the lateralization or localization of their underlying pathology or suspected seizure focus. On the whole, the former methodologies tend to study the psychosocial impact of living with a seizure disorder, while the latter focus on cognitive and neuropsychological impairments.

At first glance, apart from the opportunities to delineate the cognitive characteristics of existing and yet to be discovered genetic epilepsies, it may appear that the new classification has little to offer clinicians and researchers studying other aspects of the neuropsychological impact of epilepsy in adults. The distinction between those who experience focal vs generalized seizures is often already implicit in neuropsychological study methodologies which typically recruit highly homogenous groups, both in terms of their underlying pathology and seizure type. Unilateral or bilateral seizure onsets are important distinctions from a neurophysiological perspective, but they allow seizures arising from the right hippocampus in one person to be classified together with those arising from the same structure on the left in another. While neurophysiologically similar, there is a gulf in complexity between seeing the brain as a generator of abnormal electrical waves to a generator of thoughts and behavior. From a neuropsychological perspective, whether the seizures are arising from the language dominant or nondominant hemisphere is critical in determining the associated neuropsychological profile. The nature, age, and location of the underlying pathology will interact with genetic, clinical, and demographic factors to shape any interictal neuropsychological sequelae [15]. Neuropsychologists are unlikely to move away from the considerable body of work that has established these relationships over the past six decades to revert to the basic classifications of focal vs generalized seizures and genetic vs structural/metabolic vs unknown to classify the participants in their studies.

However, the new classification introduces the reconceptualization of focal and generalized seizures arising from a disease of brain networks. As observed in the call for papers for this special issue, 'this change

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