

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

Sallie Baxendale <sup>a,c,\*</sup>, Pamela Thompson <sup>b,c</sup>

<sup>a</sup> *Department of Clinical and Experimental Epilepsy, Institute of Neurology, UCL, UK*

<sup>b</sup> *Epilepsy Society, Chalfont St Peter, Buckinghamshire, UK*

<sup>c</sup> *University College Hospital, London, UK*

## 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.

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

## 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 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 brings a fundamental shift to our thinking about the co-morbidities of epilepsy'* [13]. As part of the network approach, changes in cognition and behavior are seen as a fundamental manifestation of the diseased network [16]. This approach encourages a move away from the almost phrenological approach characterized in some of the literature, driven by a quest

to discover the tests most sensitive to pathology within specific brain structures [15,17–19] towards a more phenotypical approach to the analysis and understanding of neuropsychological impairments in epilepsy [20,21].

#### 4. Neuropsychological phenotypes in epilepsy

The phenotypical approach has been pioneered by Hermann and his colleagues who in 2007 [20] were among the first to move on from the trend of correlating neuropsychological scores with quantified measures of brain pathology, such as hippocampal volumes or cell counts in resected specimens [22–26], recognizing the significant individual variations that were seen in people with temporal lobe epilepsy, and that these variations were typically masked in group comparison designs. Hermann et al. designed a study to see whether distinct cognitive phenotypes could be identified in temporal lobe epilepsy. A cluster analysis revealed three distinct cognitive profiles with approximately half of the group demonstrating minimal impairment on standardized cognitive tests, a quarter who had memory impairments in the context of otherwise generally intact cognitive function, and the remainder who had far more widespread impairments in memory, executive function, and processing speed. The three groups exhibited different patterns of results on demographic, clinical epilepsy, brain volumetrics, and cognitive course over a 4-year interval. In a follow-up study, Dabbs et al. [27] characterized the specific neuroanatomical abnormalities associated with each phenotype. Multiple measures of cortical thickness and brain volume distinguished the different cognitive phenotypes in a generally stepwise fashion, with the most intact cognitive profiles associated with the most normal measures of neuroanatomy and the most widespread cognitive deficits associated with the most abnormal anatomy. Cognitive phenotype is not associated with epilepsy syndrome but is associated with increasing abnormalities in brain structure, parental IQ, and features of early developmental history in children with epilepsy [21].

Thus it appears that while we can utilize the phenotypical approach reflected in the new concept for classifying the epilepsies to examine cognition and behavior in adults with epilepsy, neuropsychological studies will need to continue to consider finer distinctions within the classification framework in their quest to understand brain-behavior relationships in people with epilepsy.

#### 5. Conclusions

The revised terminology and concepts for the organization of seizures and

epilepsy proposed by the ILAE Commission on Classification and Terminology allow for a number of new opportunities in the study of cognition and behavior in adults. The first is relatively straightforward; the recognition of genetic epilepsies opens up a new field of study for neuropsychology, examining the behavioral and cognitive correlates of genetic syndromes. While much of this research to date has focused on childhood epilepsies, many of these children become adults, and the study of developmental outcomes will blend into the adult literature in time. However, the disparate findings from the limited literature on the behavioral and cognitive correlates of genetic epilepsy syndromes emphasize that genetic influences are just one strand in understanding cognition and behavior. Nevertheless, it is likely that neuropsychologists will work increasingly closely with geneticists in the study of cognition and behavior in the future and not just in the world of epilepsy.

In addition to the new classification of genetic epilepsy, the revised terminology also emphasizes a phenotypical approach to classification. Studies of behavior and cognition in epilepsy have begun to move away from matching scores on tests to pathology with discrete brain structures toward these more complex, network models of understanding.

Studies in the future will require creativity and possibly a move away from the 'domain' lead models of deficit identification to broader definitions of cognitive dysfunction which may include longitudinal patterns of decline or other patterns of variability within a profile over time. A phenotypical approach will present a significant challenge to the interpretation of scores on traditional tasks in a clinical setting, in addition to the more complex methods that will need to be employed in the research literature. It is hoped that the phenotypical approach will lead to broad collaborations between neuropsychologists and researchers working in genetics and functional imaging to really make the most of the opportunities the new classification offers.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

## References

- [1] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010; 51:676–85.
- [2] Luders HO, Amina S, Baumgartner C, Benbadis S, Bermeo-Ovalle A, Devereaux M, et al. Modern technology calls for a modern approach to classification of epileptic seizures and the epilepsies. *Epilepsia* 2012;53:405–11.
- [3] Panayiotopoulos CP. The new ILAE report on terminology and concepts for the organization of epilepsies: critical review and contribution. *Epilepsia* 2012;53: 399–404.
- [4] Engel Jr J. Report of the ILAE classification core group. *Epilepsia* 2006;47: 1558–68.
- [5] Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde BW, Engel Jr J. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia* 2001;42:1212–8.
- [6] Battaglia D, Ricci D, Chieffo D, Guzzetta F. Outlining a core neuropsychological phenotype for Dravet syndrome. *Epilepsy Res* 2016;120:91–7.
- [7] Dravet C. The core Dravet syndrome phenotype. *Epilepsia* 2011;52(Suppl 2):3–9.



- [8] Mignot C, von SC, Nava C, Ville D, Sanlaville D, Lesca G, et al. Genetic and neurodevelopmental spectrum of SYNGAP1-associated intellectual disability and epilepsy. *J Med Genet* 2016;53:511–22.
- [9] Vignoli A, La BF, Peron A, Turner K, Vannicola C, Sacconi M, et al. Autism spectrum disorder in tuberous sclerosis complex: searching for risk markers. *Orphanet J Rare Dis* 2015;10:154.
- [10] Chowdhury FA, Elwes RD, Koutroumanidis M, Morris RG, Nashef L, Richardson MP. Impaired cognitive function in idiopathic generalized epilepsy and unaffected family members: an epilepsy endophenotype. *Epilepsia* 2014;55:835–40.
- [11] van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Genotype and cognitive phenotype of patients with tuberous sclerosis complex. *Eur J Hum Genet* 2012;20:510–5.
- [12] Wood AG, Saling MM, Fedi M, Berkovic SF, Scheffer IE, Benjamin C, et al. Neuropsychological function in patients with a single gene mutation associated with autosomal dominant nocturnal frontal lobe epilepsy. *Epilepsy Behav* 2010;17:531–5.
- [13] Passamonti C, Petrelli C, Mei D, Foschi N, Guerrini R, Provinciali L, et al. A novel inherited SCN1A mutation associated with different neuropsychological phenotypes: is there a common core deficit? *Epilepsy Behav* 2015;43:89–92.
- [14] Valente KD, Rzezak P, Moschetta SP, de VS, Coan AC, Guerreiro CA. Delineating behavioral and cognitive phenotypes in juvenile myoclonic epilepsy: are we missing the forest for the trees? *Epilepsy Behav* 2016;54:95–9.
- [15] Baxendale S, Thompson P. Beyond localization: the role of traditional neuropsychological tests in an age of imaging. *Epilepsia* 2010;51:2225–30.
- [16] Wilson SJ, Baxendale S. The new approach to classification: rethinking cognition and behavior in epilepsy. *Epilepsy Behav* 2014;41:307–10.
- [17] Barr WB, Chelune GJ, Hermann BP, Loring DW, Perrine K, Strauss E, et al. The use of figural reproduction tests as measures of nonverbal memory in epilepsy surgery candidates. *J Int Neuropsychol Soc* 1997;3:435–43.
- [18] Gargaro AC, Sakamoto AC, Bianchin MM, Geraldi C, Scorsi-Rosset S, Coimbra ER, et al. Atypical neuropsychological profiles and cognitive outcome in mesial temporal lobe epilepsy. *Epilepsy Behav* 2013;27:461–9.
- [19] Kneebone AC, Lee GP, Wade LT, Loring DW. Rey Complex Figure: figural and spatial memory before and after temporal lobectomy for intractable epilepsy. *J Int Neuropsychol Soc* 2007;13:664–71.
- [20] Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. *J Int Neuropsychol Soc* 2007;13:12–20.

- [21] Hermann BP, Zhao Q, Jackson DC, Jones JE, Dabbs K, Almane D, et al. Cognitive phenotypes in childhood idiopathic epilepsies. *Epilepsy Behav* 2016;61:269–74.
- [22] Baxendale SA, van PW, Thompson PJ, Connelly A, Duncan JS, Harkness WF, et al. The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998;39:158–66.
- [23] Griffith HR, Pyzalski RW, Seidenberg M, Hermann BP. Memory relationships between MRI volumes and resting PET metabolism of medial temporal lobe structures. *Epilepsy Behav* 2004;5:669–76.
- [24] Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. *Ann Neurol* 1992;31:629–37.

[25]

Sass KJ, Sass A, Westerveld M, Lencz T, Novelly RA, Kim JH, et al. Specificity in the correlation of verbal memory and hippocampal neuron loss: dissociation of memory, language, and verbal intellectual ability. *J Clin Exp Neuropsychol* 1992;14:662–72.

[26] Sass KJ, Westerveld M, Buchanan CP, Spencer SS, Kim JH, Spencer DD. Degree of hippocampal neuron loss determines severity of verbal memory decrease after left anteromesiotemporal lobectomy. *Epilepsia* 1994;35:1179–86.

[27] Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. *Epilepsy Behav* 2009;15:445–51.