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Special Communication

Reprint of: The new approach to classification: Rethinking cognition and behavior in epilepsy☆

Sarah J. Wilson [a,b,*], Sallie Baxendale [c]

[a] Melbourne School of Psychological Sciences, The University of Melbourne, Victoria, Australia
[b] Comprehensive Epilepsy Program, Austin Health, Victoria, Australia
[c] Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, NIHR University College London Hospitals Biomedical Research Centre, London, UK

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ABSTRACT

There has been considerable debate surrounding the benefits and drawbacks of the new approach to classifying the epilepsies released by the ILAE Commission on Classification and Terminology (2005–2009). This new approach has significant implications for the way we conceptualize and assess cognition and behavior in epilepsy; however, as yet, there has been limited discussion of these issues in the field. The purpose of this Targeted Review is to spark this discussion by encouraging researchers and clinicians to think about the changes that the new approach may bring. These may include (i) reframing the way we think about the comorbidities of epilepsy, (ii) more precisely characterizing the cognitive and behavioral phenotypes of electroclinical syndromes, (iii) more carefully mapping the longitudinal trajectory of cognitive and behavioral features relative to the timing of seizures, and (iv) considering the links between cognitive, behavioral, and neurological phenotypes in the new classification scheme. It is hoped that such changes will aid translation of the advances in cognitive and behavioral neuroscience into routine clinical practice by providing purer markers of disease and more targeted treatments. A Special Issue canvassing such issues will be forthcoming that will consider current knowledge of the cognitive and behavioral features of the epilepsies from the view of the new classification scheme.

1. The new approach to the classification of the epilepsies

In 2010, the ILAE Commission on Classification and Terminology (2005–2009) published a special report recommending a fundamental shift in our understanding of concepts, use of terminology, and approach to classifying seizures and the various forms of epilepsy [1]. The rationale for this shift was to produce a more flexible organization for classifying the epilepsies that could readily incorporate our rapidly advancing knowledge in basic and clinical neuroscience to facilitate its translation to clinical epilepsy practice. The Commission proposed the adoption of a descriptive or *phenomenological* approach to achieve this flexibility [1], akin to the naturalistic approach that Charles Darwin so successfully applied to the classification of the species [2]. By contrast, the old organization was considered overly reliant on "expert opinion and assertion-dominated arguments" [1] that have diminishing adaptive value in a modernized taxonomy of the epilepsies.

Core to the new organization for classifying the epilepsies are dimensions of categorization that represent useful natural classes that are capable of reflecting current knowledge in the basic and clinical sciences. This has the effect of allowing the epilepsies and their causes to be organized in terms of multiple dimensions or features, providing choice around the consideration of features depending on one's needs and purposes [3]. Ideally, each feature should refer to a single quality rather than a mixture of different concepts and dimensions [1] to allow characterization of the observed phenomenon as precisely as possible. With the careful characterization of multiple features, this then promotes "… a flexible, multidimensional catalog of features for organizing information about different epilepsies (or seizures) as appropriate for purposes of drug development, clinical and basic research, and of course, clinical practice [1]."

2. Rethinking cognition and behavior in epilepsy

From the perspectives of clinical neuropsychology and cognitive and behavioral neuroscience, perhaps the most profound impact of the new descriptive approach is the explicit reconceptualization of focal and generalized seizures as arising out of a *disease of brain networks*, the cause of which may be genetic, lesion-based, or unknown. Focal seizures are conceived as originating in a network confined to one hemisphere that may be cortical or subcortical, discrete, or more widely distributed.

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* Corresponding author at: Melbourne School of Psychological Sciences, The University of Melbourne, Victoria 3010, Australia. Tel.: +61 3 8344 6377; fax: +61 3 9347 6618.
E-mail address: sarahw@unimelb.edu.au (S.J. Wilson).

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By contrast, generalized seizures arise within, and rapidly engage bilaterally distributed networks that again can include cortical and subcortical structures but need not be symmetric or include the entire cortex [1].

This change brings a fundamental shift to our thinking about the 'comorbidities' of epilepsy, allowing, for the first time, explicit differentiation between what might be 'essential comorbidities' from 'secondary effects'. Essential comorbidities presuppose a shared common mechanism with the epilepsy [4] and provide us with an important opportunity to move away from thinking about cognition and behavior principally in terms of secondary effects of seizures or an epileptogenic lesion towards a more fundamental manifestation of the diseased network itself. Stated another way, if epilepsy is a disease of brain networks and cognition and behavior are the primary functions of those networks, then epilepsy may be as much a disorder of cognition and behavior as it is of seizures, with cognitive and behavioral symptoms either predating seizures, or vice versa. Indeed, for some, the cognitive and behavioral symptoms may represent the most frequent and intrusive manifestation of the underlying disease, while seizures may be infrequent.

This fundamental shift in thinking opens the way for advances in cognitive and behavioral neuroscience to be more directly incorporated into clinical practice. For instance, the development of precise neurocognitive markers of network dysfunction derived from basic neuroscience or clinical research could represent a natural class of features that add an important new dimension to the classification system, with these markers serving as features of classification that could aid diagnosis or the appropriate choice of treatment. These markers would also complement already established knowledge of the secondary effects of seizures [5] and could be considered in terms of their interactions with these secondary effects. For instance, the cognitive side effects of anticonvulsant medication, disturbed sleep, or seizure-related head injuries, such as slowed mentation or poor attentional function, may exacerbate the essential cognitive manifestation of the diseased network by contributing additional cognitive load to an already compromised system. Understanding this would be vital for planning optimal treatment strategies that take account of the essential cognitive or behavioral comorbidity so as not to exacerbate its effect and, where available, for selecting treatments that target both the seizures and the essential comorbidity. Conceivably, this approach could encourage the development of new therapies that target the diseased network in more precise ways yet produce beneficial cognitive and seizure effects. Alternatively, it may foster routine use of multipronged and cross-disciplinary treatment strategies, promoting a more holistic approach to patient care.

2.1. Adopting a phenomenological approach to cognition and behavior in epilepsy

Applying a phenomenological approach to the classification of seizures, cognition, and behavior as symptoms of a diseased epilepsy network allows us to 'step back' and reconsider our understanding of cognition and behavior through the prism of the new classification system. Specifically, a phenomenological approach requires a detailed account of the cognitive and emotional processes mediated by particular brain networks and their interactions, including the way in which these processes lead to different behavioral states. Since performance on many of our current cognitive and psychological tests is determined by multiple factors, this challenges us to think about new ways of developing more precise neurocognitive and neurobehavioral markers that are designed to tap dysfunction in specific brain networks. Such markers would have clear benefits for the localization and lateralization of the epileptogenic network, thereby assisting with diagnosis, prognosis, and the choice of optimal treatment.

In terms of the electroclinical syndromes of epilepsy, a phenomenological approach would provide a more exact account of the cognitive and behavioral features that accompany specific syndromes, improving differential diagnosis and treatment. In addition to characterizing the *nature* of these specific features relative to the ictus, such an account should ideally also describe their onset, duration, and severity at different phases of the lifespan. Considered in this way, an obvious implication of the new classification system is the need to precisely characterize the cognitive and behavioral phenotypes of specific syndromes, which could assist the identification of causes, be they genes or other etiologies, and facilitate a fuller understanding of the neurobiology of specific syndromes.

2.2. Disturbed cognition or behavior as the initial or 'primary' symptom of epilepsy

It is now well recognized that disturbances in psychological function, cognition, or behavior can precede the onset of seizures and may represent the initial manifestation of the disease [6–8]. This leads to the idea that there may be specific neurocognitive or neurobehavioral markers of *disease onset* that have a temporal relationship with seizure onset. Characterization of these markers would have significant prognostic value and, arguably, could lead to the development of preventative treatments for cognitive or behavioral disturbance and, possibly, the onset of seizures themselves. In this way, it is conceivable that, in some patients, cognitive or behavioral disturbance may present as primary symptoms of an epilepsy syndrome, followed by seizures arising from the same diseased brain network. In other patients, the reverse scenario may be true, with seizures presenting as the first symptom. These scenarios give rise to important and as yet unaddressed questions about the mechanisms that may differentiate these two presentations and whether they constitute distinct epileptic phenomena or syndromes.

In terms of the new organization for classifying the epilepsies, a clear implication is the need for careful mapping of the longitudinal trajectory of psychological, cognitive, and behavioral features relative to the timing of seizures and the functioning of the affected brain network(s) in order to more accurately understand the mechanisms involved. Framing cognition and behavior as primary symptoms of epilepsy implies that the categorization of their effects can be key to classification. This means that we have the opportunity to more closely link cognitive and behavioral phenotypes with their neurological phenotypes in the new classification scheme. Considered in this light, a key challenge facing the field is to conceptualize and then phenotype the epilepsies in terms of their neurological, cognitive, or behavioral effects in order to better understand and treat cognitive, behavioral, and seizure expression in the affected network. Thinking in this way illustrates how a descriptive classification system that avoids the use of 'opaque' medical terms can facilitate new and productive lines of research inquiry [1].

3. The benefits of aligning cognitive, behavioral, and neurological phenotypes

Within the field, it has been increasingly recognized that traditional clinical practice is becoming 'out of step' with the rapid advances in cognitive and behavioral neuroscience. For this reason, a special international workshop was convened in Toronto in 2010 under the auspices of the ILAE. The express purpose of this workshop was to review and advance evidence-based neuropsychological practice for pediatric and adult patients with epilepsy by bringing together a range of specialists with expertise in adult and pediatric neuropsychology, psychiatry, neurology, neuroimaging, cognitive neuroscience, electrophysiology, pharmacology, and other fields [9]. At this meeting, it was noted that "Major developments in cognitive neuroscience and the vast number of clinical studies on epilepsy, cognition and mind have not found their way into routine clinical practice." [9]. Moreover, the critical role that clinical neuropsychology has played in epilepsy surgery has not always been expanded into the routine care of patients with epilepsy more generally [9]. Three years later, the same situation was clear at the Neuropsychology Task Force meeting of the ILAE Diagnostic Commission (2013–2017) held in Washington D.C.