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Commentary on: Motamedi, G. & Meador, K. Epilepsy and Cognition. *Epilepsy & Behavior*, 2003, 4:S25–S38

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This review paper by Motamedi and Meador consolidated nearly 20 years of prior research on cognition in epilepsy by: 1) highlighting the role of various disease attributes in the neuropsychological and behavioral functioning of patients with epilepsy and 2) discussing the potential impact of epilepsy treatments on cognitive and behavioral functioning and quality of life. Furthermore, the authors outlined important age-related factors and discussed potential approaches to treating cognitive dysfunction in patients with epilepsy. Finally, methodological pitfalls of existing research and the need to consider cognitive and behavioral risk factors when making treatment decisions were highlighted.

What is the clinical and conceptual importance in this area of investigation?

This review underscored the multifactorial nature of neurobehavioral dysfunction in patients with seizure disorders and provided useful suggestions to maximize cognitive functioning and quality of life. Cognitive and behavioral dysfunction are very common in individuals with epilepsy and can have a marked impact on quality of life. As such, it is essential that clinicians understand the factors that contribute to these comorbidities. This clinically important review paper provided broad coverage on this topic. Specifically, the key factors that impact cognition and behavior in patients with seizure disorders, ranging from biological features (e.g., seizure type/etiology, underlying neuropathology/structural cerebral damage, type and extent of intra and interictal dysfunction), to seizure-related variables (e.g., seizure frequency/severity, age at seizure onset, duration of epilepsy), to psychosocial issues (e.g., depression, anxiety, ADHD) were summarized. This paper also reviewed neurobehavioral findings across the lifespan from prenatal development to old age and summarized the neurobehavioral features of epilepsy from time of first diagnosis through a host of potential treatments, ranging from single antiepileptic drug therapy to epilepsy surgery. The authors provided a review of the neurobehavioral side effects of common AEDs including a quick reference table summarizing the cognitive effects of AEDs and the relative effects of various agents from comparative studies. Perhaps most importantly, this paper provided practical suggestions for physicians to tailor treatments so as to minimize neurobehavioral dysfunction in their patients.

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Why has this article been cited/downloaded with such high frequency?

This paper provided an opportunity for “one stop shopping,” so to speak. By consolidating over two decades of prior research, the authors provided readers with a clear, concise summary of the state of knowledge about cognition in epilepsy in 2003. It has likely served as a key reference for epilepsy researchers and clinicians by covering a vast amount of information in one quick and easily read document. It also imparted useful suggestions for expanding future research and reducing cognitive morbidity in patients with seizure disorders. The summarized information provided an excellent reference for anyone – clinician, research, student, or patient – wanting to learn more about cognition in epilepsy.

What have been the developments since publication?

Many of the findings reviewed in this 2003 publication have been subsequently replicated and/or extended and continue to be applicable today. Therefore, this article remains a useful reference. However, there have been some methodological improvements within this area of study as well as a number of new or expanded areas of research that have emerged over the past decade, furthering our knowledge regarding the neurobehavioral aspects of epilepsy. Several such advancements are briefly reviewed here.

As Motamedi and Meador noted in their 2003 review, methodological pitfalls in research on cognition at that time included inconsistency in neuropsychological batteries across studies and inclusion of measures with limited sensitivity to cognitive change. Researchers in this area have begun to shift to be more cognizant of such methodological issues. In 2006, the National Institute of Neurological Disorders and Stroke (NINDS) initiated the Common Data Elements (CDE) project “to standardize the collection of investigational data in order to facilitate comparison of results across studies and more effectively aggregate information into significant metadata results”[1]. Specific CDEs have been established across nine content areas [2, 3], including neuropsychology [4], to serve as a first step in establishing collaborative research initiatives that will pool data across many epilepsy centers to answer important clinical questions using large, diverse patient samples [4]. Further, reliable methods for assessing cognitive change over time (i.e., reliable change indices and standardized regression-based change scores), which were first developed for use in patients with epilepsy in the early 90s [5–8], have been more consistently applied to epilepsy studies in recent years. These statistical methods are important in that they control for factors that may impact cognition over time independent of any treatment effect (e.g., test-retest reliability, measurement error, regression toward the mean, practice effects). Their incorporation into epilepsy research has allowed researchers to examine cognitive and behavioral outcomes following treatment interventions, particularly epilepsy surgery, at the individual level and highlighted the limitations inherent in group comparisons that do not account for statistical artifact [9, 10].

In addition to these methodological improvements, there have been a number of areas of new or expanded research on cognition in epilepsy. Research over the past decade has clearly shown that cognitive deficits and behavioral difficulties are common in children and adults with newly diagnosed epilepsy, even prior to the initiation of antiepileptic

medications [11–15]. Further, there is evidence to suggest that these deficits often antedate the first seizure [11, 12, 16–18]. These findings indicate that underlying neurobiological factors are at work well before the first seizure emerges, and new studies have been developed to identify these factors and characterize the natural history of cognition in these patients. One such study, initiated in 2007 as part of a larger clinical trial, has revealed that in addition to having a host of cognitive deficits before AEDs are initiated, newly diagnosed adults show subtle declines in cognition over time that are not observed in healthy controls [19].

Research on the neurobehavioral impact of antiepileptic drugs has continued since the publication of “Epilepsy and Cognition,” and many of the findings summarized in this paper have been replicated and/or extended [20–24]. While it has been long known that antiepileptic medications taken during pregnancy can have a negative impact on fetal neurodevelopment, this area of research has greatly expanded in recent years. The cognitive impact of in utero exposure to AEDs over the course of early development (up to 6 years of age) has recently been documented in a series of publications derived from two large-scale prospective studies: the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study and the Liverpool and Manchester Neurodevelopmental Group (LMNDG). After controlling for relevant covariates, results suggest an increased risk for cognitive impairment in children exposed to valproate or AED polytherapy [25–31]. Children exposed to valproate in utero are also at higher risk for neurodevelopmental disorders, including autism spectrum disorders and ADHD, and show poorer adaptive functioning [32–35].

Technological advances over the past decade have also resulted in a number of new or improved methods for assessing and understanding language and cognition in patients with epilepsy. Less invasive methods for assessing language lateralization and localization (e.g., functional MRI, magnetoencephalography, functional near infrared spectroscopy) are being used with increasing frequency resulting in a marked reduction in the use of the Wada test among surgical candidates [36, 37]. Advances in neuroimaging (e.g., resting state fMRI, diffusion tensor imaging) have greatly expanded our knowledge regarding the functional connectivity of various brain regions and how they relate to cognitive function and dysfunction in epilepsy [38–41].

With the availability of advanced sequencing technologies at reduced cost, genetic research in epilepsy has also expanded very rapidly over the past decade. Genetic anomalies, many associated in sodium channel mutations, have been identified in a number of seemingly disparate epilepsy syndromes that involve intellectual disability or other cognitive dysfunction [42]. Two large-scale, international collaborative efforts, Epi4K and Epilepsy Phenome/Genome Project, have been launched in recent years to investigate the genetic basis of epilepsy and response to treatment [43, 44]. These studies will be important in paving the way for future research investigating the role of genomic factors in many aspects of epilepsy. Genetic factors clearly influence brain structure and function and contribute to the cognitive and behavioral phenotypes observed in individuals with epilepsy. Research in this area has only just begun and the role of genetic factors in cognition and behavior in epilepsy remains largely unknown at this time [45].

Conclusions

The “Epilepsy and Cognition” paper by Motamedi and Meador highlighted the high frequency of cognitive and behavioral difficulties in patients with epilepsy and outlined potential contributing factors. While aspects of the seizure disorder itself and the underlying etiology are associated with neurobehavioral dysfunction, treatment interventions aimed at reducing seizure burden and psychosocial factors may also play an important role. Physicians were advised to be aware of the risk factors for cognitive and behavioral morbidity and individualize treatments to minimize cognitive and behavioral side effects. This is an important review article that summarized a vast amount of information into an easy to read reference guide. Thus, it is not surprising that it is one of the top 10 cited papers published in *Epilepsy & Behavior* since its inception 15 years ago.

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