*Journal of the International Neuropsychological Society* (2017), **23**, 791–805.

doi:10.1017/S1355617717000650

# Paradigm Shifts in the Neuropsychology of Epilepsy



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(RECEIVED March 2, 2017; FINAL REVISION June 5, 2017; ACCEPTED June 11, 2017)

**Abstract**

This article reviews the major paradigm shifts that have occurred in the area of the application of clinical and experimental neuropsychology to epilepsy and epilepsy surgery since the founding of the International Neuropsychological Society. The five paradigm shifts discussed include: 1) The neurobiology of cognitive disorders in epilepsy – expanding the landscape of syndrome-specific neuropsychological impairment; 2) pathways to comorbidities: bidirectional relationships and their clinical implications; 3) discovering quality of life: The concept, its quantification and applicability; 4) outcomes of epilepsy surgery: challenging conventional wisdom; and 5) Iatrogenic effects of treatment: cognitive and behavioral effects of antiepilepsy drugs. For each area we characterize the status of knowledge, the key developments that have occurred, and how they have altered our understanding of the epilepsies and their management. We conclude with a brief overview of where we believe the field will be headed in the next decade which includes changes in assessment paradigms, moving from characterization of comorbidities to interventions; increasing development of new measures, terminology and classification; increasing interest in neurodegenerative proteins; transitioning from clinical seizure features to modifiable risk factors; and neurobehavioral phenotypes. Overall, enormous progress has been made over the lifespan of the INS with promise of ongoing improvements in understanding of the cognitive and behavioral complications of the epilepsies and their treatment. (*JINS*, 2017, *23*, 791–805)

**Keywords:** Epilepsy, Neuropsychology, Behavior

## INTRODUCTION

Neuropsychology and epilepsy have enjoyed a long and mutually beneficial relationship (Loring, 2010; Novelly, 1992). The epilepsies have provided a window to advance understanding of brain function, producing insights into the effects of focal epilepsies and their surgical intervention, leading to a greater understanding of the brain mechanisms underlying a wide variety of cognitive and behavioral constructs (Elger et al., 2004; Jones-Gotman et al., 2010). Neuropsychology has also played an important clinical role by characterizing the impact of epilepsy through its relationship with factors such as age of onset of epilepsy, etiology, seizure type and syndrome, medications, duration of epilepsy, and electroencephalographic (EEG) abnormalities (Dodrill & Matthews, 1992; Folsom, 1952; Helmstaedter & Witt, 2012; Tarter, 1972; Trimble & Thompson, 1986; Vermeulen & Aldenkamp, 1995).

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In this review, we focus on important advances that have occurred in the field of neuropsychology and epilepsy from the time of the formation of the International Neuropsychological Society in 1967 to the present, or some 50 years. The advances to be described include a brief synopsis of the state of the field antecedent to these developments and their impact going forward, along with examples of key studies that changed the paradigms of the time. We conclude with a brief discussion of what we think the future holds for clinical and research directions in the neuropsychology of epilepsy.

## NEUROBIOLOGY OF COGNITIVE DISORDERS IN EPILEPSY: EXPANDING THE LANDSCAPE OF SYNDROME-SPECIFIC NEUROPSYCHOLOGICAL IMPAIRMENT

The characterization and nosology of seizures and epilepsy syndromes has evolved through the decades, with initiation of formal efforts to construct an internationally agreed classification system in the 1960s, with ongoing modifications based on new knowledge (Berg et al., 2010; Scheffer et al., 2017;

Wolf, 2009). Focal or localization-related epilepsies are commonly characterized in terms of their lobar site of origin, and neuropsychology has historically focused on structure–function relationships such as executive function in frontal lobe epilepsy (FLE) and memory in temporal lobe epilepsy (TLE).

The critical distinctions between declarative and procedural memory systems were demonstrated by Milner through careful study of patient H.M. (Milner, 1965), with the later development of the material-specific model of anterograde memory (Milner, 1972). This model posited that, if seizure onset originated from the language dominant temporal lobe, then verbal learning and memory would be adversely affected. Although somewhat less robust, if seizure onset occurred in the nondominant temporal lobe, learning and memory for non-verbal material such as designs or faces would be affected with largely spared verbal memory (Barr, 1997). Other cognitive abilities were expected to be relatively unaffected because both seizure onset and focal epileptiform abnormalities were restricted to the temporal lobe structures that encoded new memories.

Studies began to accumulate, however, demonstrating that both cognitive and brain abnormalities associated with the focal epilepsies could extend beyond the seizure onset zone. Although memory impairments are a common feature of TLE related to hippocampal neuronal loss and sclerosis, they occurred against the backdrop of more distributed cognitive abnormality affecting not only memory, but also IQ, executive functions, language, sensorimotor, and other abilities (e.g., Agah et al., 2017; Baxendale & Thompson, 2010; Glosser et al., 1997; Guimaraes et al., 2007; Oyegbile, Dow, et al., 2004; Rzezak et al., 2007; Stretton & Thompson, 2012; Wang et al., 2009).

Similarly, genetic generalized epilepsies (GGE) were thought to have neuropsychological deficits restricted to attention and executive function, but a recent meta-analysis of patients with GGE, including juvenile myoclonic epilepsy, demonstrated impairment in all cognitive domains except for visuospatial abilities and, of note, without disproportionate impairment of executive function (Loughman, Bowden, & D'Souza, 2014). Likewise, neuropsychological impairments may be broader than anticipated in FLE and related to distributed brain anomalies (Braakman et al., 2012, 2014, 2015), with distinctions between focal epilepsy syndromes in children with epilepsy (e.g., temporal versus frontal) often less crisp than believed, this due to several factors including the impact of epilepsy on neurodevelopmental processes (Smith, 2016).

Neuroimaging studies have documented a similar pattern of distributed abnormalities in brain networks associated with focal epilepsies. For example, distributed morphometric abnormalities in "normal" clinical MRIs began to be reported in surgical patients with TLE with hippocampal sclerosis which were found to be associated not only with poorer surgical outcome (Sisodiya et al., 1997) but also with adverse cognitive (memory) outcomes (Baxendale et al., 1999). Neuroimaging research using diverse techniques documented the range of abnormalities extending beyond the epileptogenic temporal lobe to ipsilateral extra-temporal regions, the contralateral hemisphere, and subcortical structures and cerebellum (Keller & Roberts, 2008).

These abnormalities included diffusely distributed cortical thinning (Keller et al., 2015; Lin et al., 2007; McDonald et al., 2008), other bilateral anomalies in cortical surface features (Oyegbile, Magnotta, et al., 2004), as well as distributed abnormalities in white matter volumes and connectivity (Alhusaini et al., 2012; Hermann et al., 2003; Mueller et al., 2006; Otte et al., 2012; Ronan et al., 2007; Seidenberg et al., 2005; Slinger, Sinke, Braun, & Otte, 2016), these effects often more pronounced in patients with the syndrome of mesial temporal lobe epilepsy. Postmortem neuropathological investigations of TLE patients are pertinent and consistent in this regard as well (Blanc et al., 2011; Margerison & Corsellis, 1966; Sinjab, Martinian, Sisodiya, & Thom, 2013).

While early structure-function investigations in TLE focused on relationships between hippocampal atrophy and memory (Lencz et al., 1992; Trenerry et al., 1993), subsequent studies reported a wider range of brain-behavior links such as associations between frontal abnormality with executive function (Keller, Baker, Downes, & Roberts, 2009), the numerous studies of this type cumulatively informing an evolving neurobiological architecture of cognitive impairment in TLE (Hermann, Lin, Jones, & Seidenberg, 2009).

This paradigm shift recognized that the landscape of cognitive abnormality within a localization related epilepsy was not driven solely by the location of the epilepsy, but by the nature, range and severity of underlying distributed neurobiological abnormalities (Bell, Lin, Seidenberg, & Hermann, 2011), the etiology and course of which continues to intensely investigated (Rayner, Jackson, & Wilson, 2016a). Cognitive abilities depend on distributed neural networks and the degree to which these networks are characterized and how they are impacted by epilepsy will be a major path of investigation going forward (McDonald et al., 2014).

## PATHWAYS TO COMORBIDITIES: BIDIRECTIONAL RELATIONSHIPS AND THEIR CLINICAL IMPLICATIONS

Epilepsy patients carry a significantly elevated burden of medical/somatic, psychiatric, and social disorders in addition to cognitive difficulties (Gaitatzis, Sisodiya, & Sander, 2012; Keezer, Sisodiya, & Sander, 2016; Tellez-Zenteno, Matijevic, & Wiebe, 2005; Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007). Although the co-occurrence of these disorders with epilepsy is well documented, their causal pathways including temporal sequence are often not clear (Keezer et al., 2016). A common view has been that epilepsy including recurrent seizures, persistent interictal EEG abnormalities, treatment effects, and psychosocial factors all contribute to the development and progression of comorbid cognitive and psychiatric conditions after initial seizure onset.

A major disruption to this paradigm was the demonstration of a bidirectional relationship between epilepsy and cognitive,

psychiatric, and social comorbidities in both pediatric and adult epilepsies (Forsgren & Nystrom, 1990; Hesdorffer, 2016; Hesdorffer, Hauser, Annegers, & Cascino, 2000; Keezer et al., 2016). It began to be appreciated that psychiatric comorbidities frequently appeared before seizure onset and could represent a risk factor for subsequent epilepsy, or both could be due to a common underlying mechanism. This bidirectional relationship exists for multiple comorbid conditions including depression, suicidality, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), psychosis, and schizophrenia (Lin, Mula, & Hermann, 2012). Much remains to be learned about the potential mechanisms underlying bidirectional relationships. Kanner (2012) suggested that pertinent to the epilepsy-depression relationship may be endocrine abnormalities, structural and functional abnormalities of cortical and subcortical structures, neurotransmitter abnormalities, and/or immunological abnormalities.

Of particular interest is co-aggregation of cognitive, behavioral, and even brain structural abnormalities in the nonaffected siblings of persons with epilepsy (Alhusaini et al., 2016; Aronu & Iloeje, 2011; Badawy, Vogrin, Lai, & Cook, 2013; Chowdhury et al., 2014; Hesdorffer, Caplan, & Berg, 2012; Iqbal et al., 2015, 2009; Keller et al., 2014; Levav et al., 2002; Singhi, Bansal, Singhi, & Pershad, 1992; Smith et al., 2012; Tsai et al., 2013; Verrotti et al., 2013; Wandschneider et al., 2014, 2010). These reports suggest the presence of distinct endophenotypes, raising the possibility of shared genetic mechanisms, although the influence of environmental and other factors remain to be clarified.

Bidirectionality and conceptualizing epilepsy as a disease of brain networks raised the possibility that behavioral comorbidities may be present at the time of diagnosis. Indeed, adults and elders with new onset epilepsies display a pattern of mild diffuse cognitive impairment at diagnosis and before treatment initiation (Taylor et al., 2010; Witt & Helmstaedter, 2012; Witt et al., 2014). These patients have abnormal 1-year and 5-year cognitive courses that predominantly affect memory, executive function, and psychomotor speed (Baker, Taylor, Aldenkamp, & SANAD group, 2011; Taylor & Baker, 2010) (see Witt and Helmstaedter 2015 for review).

In children with new onset epilepsies, elevated are rates of behavioral problems including ADHD, depression and anxiety, early life histories of academic struggles and provision of supportive academic services, and a pattern of distributed cognitive anomalies that may even precede the first recognized seizure (Austin et al., 2001; Berg et al., 2005; Fastenau et al., 2009; Hoare, 1984; Oostrom, Smeets-Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2003; Overvliet, Aldenkamp, Klinkenberg, Vles, & Hendriksen, 2011; Pohlmann-Eden et al., 2015). These findings demonstrate the need for neuropsychology to be involved in the routine clinical care of epilepsy patients, screening new onset cases for pertinent comorbidities to initiate timely treatment, and following patients to monitor problematic trajectories (Wilson et al., 2015).

## DISCOVERING QUALITY OF LIFE: THE CONCEPT, ITS QUANTIFICATION, AND APPLICABILITY

Quality of life (QoL), reflected in the general wellbeing of individuals and societies, represents a core paradigm shift in the quality of care of people with epilepsy. This came about in stages. Before the availability of formal health-related quality of life (HRQOL) measures, patient status was characterized by traditional clinical interview or the use of tests that had been developed for much broader application (e.g., personality and IQ assessment). Thus, "QoL" was characterized by a mix of diverse measures representing a battery-type approach to characterize disease, treatment effects, and patient status.

Disease-specific measures were later developed to characterize unique issues influencing life with epilepsy. The most influential early epilepsy-specific measure was the Washington Psychosocial Seizure Inventory (WPSI) developed by Carl Dodrill and colleagues at the University of Washington, which assessed family background, emotional adjustment, interpersonal adjustment, vocational adjustment, financial status, adjustment to seizures, medicine and medical management, with a summary evaluation of overall psychosocial functioning (Dodrill, Batzel, Queisser, & Temkin, 1980). The WPSI was translated and used internationally, contributing to a "common language" for characterizing psychosocial complications.

The most recent stage has been the adoption of formal HRQOL logic and methods. This approach uses a general measure (e.g., the Rand 36-Item Health Survey, aka SF-36) for comparison with other conditions, supplemented by epilepsy specific items. Work in epilepsy surgery was again prominent in leading the way, with Vickrey and colleagues first developing the Epilepsy Surgery Inventory-55 (Vickrey et al., 1995). This mixed generic and disease-specific instrument was expanded into the Quality of Life in Epilepsy Inventory-89 items (QOLIE-89) (Devinsky et al., 1995) to be applicable to settings outside of epilepsy surgery with less severely affected patients.

While initial studies using HRQOL measures demonstrated that improvements after surgery were linearly related to a reduction in seizure frequency (Vickrey et al., 1995), the importance of other predictors was soon recognized, including mood, cognition, employment, driving, and antiepileptic drug (AED) cessation (for a review, see Wilson and Engel, 2010). Gilliam et al. (1999) reported a striking negative linear relationship between HRQOL and symptoms of depression; and Kanner, Barry, Gilliam, Hermann, and Meador (2010) subsequently noted that co-morbid anxiety and depression had the greatest impact on HRQOL. Also very influential was the "Liverpool school of HRQOL" (Baker, 1998; Baker, Jacoby, Buck, Stalgis, & Monnet, 1997; Baker, Smith, Dewey, Jacoby, & Chadwick, 1993; Jacoby, Snape, & Baker, 2009), demonstrating that, although *seizure frequency* was a common outcome measure in clinical trials and surgical series, *seizure severity* had been ignored. Seizure severity,

but not seizure frequency, was related to self-esteem, locus of control, and anxiety.

While HRQOL research has principally focused on improvements in well-being associated with epilepsy treatments, the Melbourne group demonstrated that the diagnosis of a first seizure gives rise to a process of losing and restoring perceived control, characterized by two psychological adjustment trajectories that hinged on the experience of a limited or pervasive loss of control, leading to different medical and HRQOL outcomes (Velissaris, Saling, Newton, Berkovic, & Wilson, 2012). The latter trajectory involves a more extensive process of personal re-evaluation and psychosocial change, akin to what occurs after trauma (Velissaris, Wilson, Saling, Newton, & Berkovic, 2007).

## OUTCOMES OF EPILEPSY SURGERY: CHALLENGING CONVENTIONAL WISDOM

The neuropsychology of epilepsy surgery has its roots in the early pioneering programs in Montreal (Penfield and Milner), London (Falconer and Meyer), and Chicago (Bailey, Gibbs, and Halstead). Epilepsy surgery was initially considered a final treatment option following many years of failed medication management and devastating psychosocial complications. The 1980s witnessed the beginning of an explosion of interest in epilepsy surgery during which time two influential international symposia occurred, the Palm Desert Workshops on Epilepsy Surgery held in 1986 and 1992 (Engel, 1987, 1993). These were transformative in fueling critical thinking about patient evaluation and selection, surgical treatments, outcome assessments, and surgery as a mainstream option to consider before decades of failed medical therapy.

### Cognitive Outcomes

A primary concern regarding anterior temporal lobectomy (ATL) is the risk of significant post-operative memory decline/amnesia (Milner, 1958), and neuropsychological practice has traditionally addressed three issues: (1) interest in the congruence of neuropsychological deficits with the area of ictal onset, (2) reliance on the material-specific model of memory function to assess whether the contralateral temporal lobe had sufficient functional capacity to sustain memory function post-operatively, and (3) assessment of post-operative memory risk using the intracarotid amobarbital (aka Wada) test.

Three developments altered this classic paradigm. First, some surgeons excised hippocampus *en bloc*, which facilitated quantitative assessment of neuronal loss and gliosis in hippocampal subfields which could then be related to preoperative memory and Wada test performance (O'Rourke et al., 1993; Rausch & Babb, 1987; Sass et al., 1991, 1992, 1990). Second, advances in MR imaging allowed non-invasive quantification of hippocampal volumes which could then be correlated with preoperative memory results (Lencz et al., 1992; Trenerry et al., 1993). MRI also allowed examination of hippocampal-memory relationships both ipsilateral and contralateral to the side of eventual surgery. Third, a logical extension of this work was examination of post-operative memory outcomes as a function of markers of ipsilateral hippocampal integrity reflected in cell counts, quantitative MRI, or adequacy of preoperative memory function. Resection of a less diseased/more functional hippocampus was found to be a primary driver of memory decline (Hermann, Wyler, Somes, Berry, & Dohan, 1992; Rausch and Babb, 1993; Sass et al., 1994), findings that continue to be reported and elaborated upon (Coras et al., 2014; Witt et al., 2015).

This changing paradigm was crystallized by Chelune (1995) in which he suggested that the *functional integrity* of the to-be-resected hippocampus, as reflected by less hippocampal atrophy, higher hippocampal cell counts, or better preoperative memory performance, was a primary mediator of pre- to postoperative memory change, rather than the *functional reserve* of the contralateral temporal lobe as initially proposed (Milner, Branch, & Rassmussen, 1962). This reformulation emphasizing ipsilateral rather than contralateral hippocampal function has influenced assessment techniques including preoperative memory assessment *via* functional MRI (fMRI), in which a strong predictor of memory decline following ATL is ipsilateral posterior hippocampus activation (Bonelli et al., 2010).

Relatedly, the material-specific memory model has been unable to account for multiple failures to link right hippocampal resection to "non-verbal" or "visual memory" declines as well as reports of mildly impaired story recall in patients with left or right mesial temporal foci (Saling et al., 1993). In a major contribution and arguably paradigm shifting proposal, Saling overviewed the historical development of the material-specific model of memory, the findings inconsistent with the model, and the logic leading to his major reformulation (Saling, 2009) that *task-specificity*, rather than *material-specificity*, is more relevant in predicting verbal memory outcomes as it reflects the intra-temporal organization of memory. In particular, Saling noted that arbitrary relational forms of learning (i.e., unrelated word pairs) appear mediated by specific potions of the left medial temporal lobe (perirhinal cortex) which can be distinguished from semantically rich forms of verbal learning (i.e., semantically loaded associations) mediated by the lateral temporal cortex (anterior inferior temporal gyrus), with potential corresponding similarities in task specific findings in the right medial and lateral temporal lobes.

Lastly, important has been the shift from characterizing cognitive outcome following surgery in groups to characterizing (and predicting) outcome at the individual level (e.g., development of reliable change indices and standardized regression-based measures). In addition to providing a more rigorous approach to assess meaningful cognitive change attributable to surgery, these methods highlighted the variability in cognitive performance observed in individuals with epilepsy over time (with or without intervening surgery) (Martin et al., 1998; Sawrie et al., 1996; Sherman et al., 2011).

### From Anterograde to Semantic Memory Systems

Also changing over this time was a greater appreciation of the impact of focal epilepsy, particularly left temporal lobe epilepsy, on semantic memory (Bell et al., 2001; Seidenberg et al., 2002; Tippett, Glosser, & Farah, 1996). Multiple reports suggested a robust relationship between decreased confrontation naming ability and left temporal seizure onset, which oftentimes exceeded the relationship between left TLE and verbal learning and memory (Busch, Frazier, Iampietro, Chapin, & Kubu, 2009). More than 40% of left ATL patients compared to only 5% of right ATL patients exhibit naming decline postoperatively (Busch et al., 2016).

TLE patients are also impaired at naming famous faces (Benke, Kuen, Schwarz, & Walser, 2013; Drane et al., 2013) and, furthermore, the naming deficits can be category dependent (Tippett et al., 1996). Interestingly, left TLE patients that display impaired confrontation naming are generally able to recognize famous faces and objects (Drane et al., 2008), whereas right TLE can be associated with recognition impairment that is thought to result from impaired processing in the ventral visual stream, reflecting a mild visual agnosia. This suggests that assessment of visual naming fails to capture the full impact of epilepsy and epilepsy surgery on the semantic memory network.

### Plasticity of the Epileptic Brain

The gold standard for establishing cerebral language dominance before epilepsy surgery has been the Wada test, which pharmacologically inactivates the region of the internal carotid artery while the patient performs multiple cognitive tasks including language and memory. This technique not only was critical for identification of language before surgery, in which language mapping or less extensive resection would typically be performed for language dominant resections, but was critical in establishing the relationship between handedness and cerebral dominance, including pathological left handedness in which early left brain lesions cause a shift in language and dominance from the predisposed left hemisphere to the right hemisphere (Rasmussen & Milner, 1977).

However, as Wada techniques became increasingly refined, they also demonstrated that exclusive right hemisphere representation was rare and that language reorganization typically existed on a continuum (Loring et al., 1990) which has now been well-described in the fMRI literature (Abbott, Waites, Lillywhite, & Jackson, 2010; Binder et al., 1996). When a shift in the biological predisposition for left cerebral language dominance occurs, it is often associated with age of injury, region of onset, and magnitude of injury (Stewart et al., 2014). A shift of language dominance, however, may occur in the absence of a shift of verbal learning and memory (Loring et al., 1990; Wood, Saling, O'Shea, Jackson, & Berkovic, 1999).

Several activation paradigms reliably identify language non-invasively (Binder et al., 1996; Gaillard et al., 2004). Reliable fMRI identification of language laterality has substantially altered the practice of the preoperative neuropsychological evaluation for epilepsy by decreasing the need for evaluation of language with the Wada test (Baxendale, 2009; Baxendale, Thompson, & Duncan, 2008). What has not yet been satisfactorily developed, however, is a valid fMRI memory task to replace the need for Wada memory testing in selected patients, but important is evidence indicating that patterns of language activation predict the risk of postsurgical verbal memory outcomes (see Szaflarski et al., 2017; Binder et al., 2010).

### Life Outcomes

A goal of epilepsy surgery has always been to improve the postoperative life of people with epilepsy (Taylor, 1993; Jones, Blocher, & Jackson, 2013). In fact, in the early days of the University of Illinois surgical program, a pioneering electroencephalographer (Frederic Gibbs) convinced a reluctant neurosurgeon (Percival Bailey) to operate solely on the basis of EEG since, without surgery, the patients' compromised quality of life would persist (Hermann & Stone, 1989). However, it may be a somewhat naïve assumption to believe that a patient with long-standing compromised cognitive, psychiatric, or social status will suddenly improve their life situation following successful surgery without broader rehabilitation efforts.

The Melbourne group identified a complex set of psychological and social changes that need to occur after surgery for a patient to maximally benefit from seizure freedom (Bladin, 1992; Wilson, Bladin, & Saling, 2001). This process, driven by a change in patient identity as they learn to "become well," gives rise to a set of psychological and social features that constitute a syndrome termed the "burden of normality." Although seizure freedom may be necessary for improved HRQOL after surgery, it is not sufficient, with patients and families also requiring post-operative rehabilitation and psychosocial support as they adapt to the new challenges of a seizure free lifestyle. This post-operative support is also critical for approximately one third of patients who experience the significant comorbidity of depression after epilepsy surgery, including suicidality and *de novo* presentations. A range of factors, including a pre-operative psychiatric history and smaller contralateral hippocampal volume, have been identified as risk factors (Wrench, Matsumoto, Inoue, & Wilson, 2011).

## IATROGENIC EFFECTS OF TREATMENT: COGNITIVE AND BEHAVIORAL EFFECTS OF ANTIEPILEPSY DRUGS

Because most epilepsy drugs have comparable efficacy in controlling seizures for appropriate epilepsy indications, differential neuropsychological effects are now commonly used by prescribing physicians to inform initial AED selection. The first systematic characterization of different AED profiles was by Dodrill and Troupin (1977), although this study was confounded by trial design issues since comparable drug levels were not contrasted.

The most influential paper reporting cognitive AED effects was the demonstration that phenobarbital used for seizure

prophylaxis after a febrile seizure was associated with FSIQs that were approximately ½ *SD* lower than placebo treated children (Farwell et al., 1990). These differences persisted following phenobarbital discontinuation indicating cumulative treatment effects from which the children were unable to catch up (Sulzbacher, Farwell, Temkin, Lu, & Hirtz, 1999). These studies, combined with the absence of benefit in decreasing subsequent seizures, contributed to current practice in which AED prophylaxis is not routine, and phenobarbital is generally avoided as a first-line epilepsy treatment.

One criticism of neuropsychological AED studies is that group differences may be difficult to apply on an individual patient basis, and studies are typically not dose-ranging. With increasing application of reliable change indices, however, epidemiological statistics such as the number needed to harm (NNH) will likely better characterize risks of cognitive impairment at different levels of AED doses (Loring, Williamson, Meador, Wiegand, & Hulihan, 2011). Several reviews of the cognitive side effects of AEDs have been published, although information on the more recently introduced medications are not included (Loring et al., 1990; Vermeulen & Aldenkamp, 1995).

Even when neuropsychological outcomes are not the primary endpoint in clinical trials, they form a component of overall treatment "effectiveness" beyond treatment "efficacy." AED differences on the Continuous Performance Task contributed to specific initial treatment recommendations for ethosuximide over valproate in treating childhood absence epilepsy since both medicines were equally effective in treating seizures (Glauser et al., 2010). Neuropsychology has also demonstrated that children exposed to valproate during their mothers' pregnancy have lower IQ than children exposed to carbamazepine, lamotrigine, or phenytoin, which has led to changes in the FDA warning label (Meador et al., 2009). Neuropsychology is now routinely used to characterize safety of new procedures and new devices, and has demonstrated a surprising finding that not only is long-term responsive neurostimulation to control epilepsy not associated with cognitive side effects, but that there may actually be a therapeutic benefit (Loring, Kapur, Meador, & Morrell, 2015).

## WHERE WILL (SHOULD) NEUROPSYCHOLOGY HEAD DURING THE NEXT DECADE?

Neuropsychology will continue to play an important role in epilepsy research and care. Although the specifics of neuropsychology's clinical and research applications will likely differ considerably from how neuropsychology is currently practiced, epilepsy neuropsychology will likely change along a common continuum shared by changes in the cognitive assessments and research trends in other diseases.

### Changes in Assessment Paradigms

We anticipate that it may become more difficult to obtain approval to conduct comprehensive neuropsychological evaluations outside the context of surgical evaluation, although changes in insurance coverage are difficult to predict. On the positive side, however, we also anticipate shorter but more routine testing of *all* epilepsy patients due to the high rates of cognitive and behavioral issues, including in new onset cases, with screening becoming a routine part of efforts designed to maximize and maintain cognitive and behavioral health. As part of routine screening, there will likely be greater reliance on computerized assessment such as the NIH Cognitive Toolbox (Weintraub et al., 2013) or the NIH PROMIS (Nowinski et al., 2016), and hopefully innovative approaches such as virtual reality tests designed to maximize ecological validity of constructs.

While some may see this as a threat to traditional clinical neuropsychological practice, we view this as an opportunity to characterize cognitive and behavioral comorbidities on a broader basis rather than through selective referrals, with screened patients meeting various thresholds of cognitive impairment continuing to require more comprehensive evaluation for effective clinical management. In our Internet age with growing interest in "big data" approaches, the time would appear right to develop large interactive databases for multicenter collaboration and research purposes. Facilitative movements in this direction have begun in Europe (Vogt et al., 2017) and within the International League Against Epilepsy (Wilson et al., 2015).

### Moving from Characterization to Intervention

The neuropsychology of epilepsy literature has been one largely of characterization of disease and treatment impacts. Although there has been increasing emphasis on screening and early identification of comorbidities, there is a clear need for systematic intervention trials to improve practice and patient outcomes. Appearing are reports of interventions designed to improve memory and cognition (Adams et al., 2017; Caller et al., 2016; Del Felice et al., 2017; Farina, Raglio, & Giovagnoli, 2015; Jackson, Makin, & Baker, 2015), mood disorders (Gandy, Sharpe, & Perry, 2013), and epilepsy self-management (Jobst & MEW network, 2017; Shegog et al., 2013; Wagner et al., 2017). Both pharmacologic and behavioral interventions will be critical to improving patient life outcomes in patients with chronic epilepsy (Del Felice et al., 2017) and those who have undergone epilepsy surgery (Mazur-Mosiewicz et al., 2015). The reviews to date have noted the numerous weaknesses and challenges inherent in these attempts, but the time appears right to move forward on major intervention efforts.

### Increasing Development of New Measures, Terminology, and Classification

Colleagues in neurology, EEG, surgery, radiology, and other fields have been rapidly developing and advancing impressive novel technologies to apply to epilepsy and its comorbidities. Neuropsychology, in contrast, has the dubious distinction of advancing via new versions of established general tests (Loring & Bauer, 2010). That said, there have been innovative inroads into new approaches to assess language function (Hamberger &

Cole, 2011), category specific naming (Drane et al., 2008), and social function (theory of mind) (Giovagnoli, 2014), which are important for epilepsy care and will influence practice and research. We also continue to lack a common language of assessment and cognitive diagnosis internationally, few common international epilepsy specific measures, and lack a cognitive taxonomy such as that used in aging and dementia, which would facilitate international communication and research. These issues will develop going forward.

Especially critical will be efforts to increase the cultural sensitivity of measures given the changing demographics across countries. Much of the existing literature on the neuropsychology of epilepsy is based on studies performed in English-speaking countries such that the assessment and research approaches available to the world are geared to that population. Initial steps to address these limitations and develop a more global approach to understanding epilepsy as it is manifested internationally has motivated neuropsychologists to address this issue with the aim to develop methodology with more universal applications (Djordjevic, 2011; Jones-Gotman et al., 2010; Ho & Lee, 2011; Saez et al., 2014; Witt & Helmstaedter, 2011).

## Increasing Interest in Neurodegenerative Proteins

Before the development of effective AEDs, "dementia" was considered an inevitable end state of chronic epilepsy, and the early epilepsy colonies frequently contained specific buildings for patients with brittle psychiatric disorders and dementia. Concern regarding disease progression, cognitive decline and development of frank disorders associated with cognitive aging is increasing (Breuer et al., 2017; Subota et al., 2017), especially in the context of the aging of the world population. Interest will increase to identify neuroimaging (e.g., Pardoe et al., 2017) and cognitive biomarkers of "progressive disease" and "accelerated aging." Assessing the proteins of neurodegeneration, including tau (Puvenna et al., 2016; Sen et al., 2007; Tai et al., 2016; Thom et al., 2011) and beta-amyloid (Joutsa et al., 2017; Mackenzie & Miller, 1994) are under way, and we anticipate more work examining the presence and distribution of neurodegenerative proteins and their relationship to cognition, cognitive change, and cognitive aging in epilepsy.

## Transitioning From Clinical Seizure Features to Modifiable Risk Factors

In the general neuropsychology literature, and especially in the Alzheimer's disease and related preclinical disease literature, a wide range of lifestyle, health, and social factors have been shown to be associated with accelerated cognitive aging and dementia. Increasing interest has focused on potentially modifiable risk factors (e.g., diabetes mellitus, hypertension, obesity, depression, physical inactivity, smoking, low education) (Barnes & Yaffe, 2011; Daviglus et al., 2010; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). These and other potentially modifiable factors are rarely examined in relation to cognition in epilepsy, although this is likely to change given the demonstrated increased prevalence of these modifiable risk factors in people with epilepsy reported in population based surveys (e.g., Kobau et al., 2008).

Work in epilepsy is beginning to appear on factors such as exercise, obesity (Baxendale et al., 2015; Hamed, 2015), vascular risk (Hamed, 2014), and metabolic abnormalities in epilepsy, sometimes examined in relation to cognitive status (Baxendale et al., 2015). These are important developments as such risk factors may affect brain as well as cognition. For example, a recent population-based investigation demonstrated association of atrophy of cerebral white matter volume with overweight and obese individuals, with maximal effects in middle-age corresponding to an estimated increase of brain age of 10 years (Ronan et al., 2016). Other population-based investigations have demonstrated elevated vascular risk factors that may explain the high risk of cerebral and cardiac vascular disease in epilepsy patients (e.g., hyperlipidemia) (Harnod, Chen, Li, Sung, & Kao, 2014), which may also be related to untoward antiepileptic medication effects (Brodie et al., 2013).

## Neurobehavioral Phenotypes

A clinical reality is that patients with any specific epilepsy syndrome exhibit significant variability in cognitive and behavioral presentations. Our notions of what to expect (memory in TLE, executive dysfunction in FLE) are useful, but often imprecise for reasons discussed previously. There may be discernible latent cognitive and behavioral groups within any epilepsy syndrome, or even latent groups that manifest across diverse epilepsy syndromes. For example, there may be patients with essentially normal cognitive profiles, severely impaired profiles, or profiles characterized by impairments in specific cognitive abilities represented within or across syndrome groups.

Identifying latent groups or phenotypes has been underused in the neuropsychology of epilepsy and would seem to be of heuristic value. Distinct latent neurobehavioral groups have been identified within JME (Valente et al., 2016), Rolandic epilepsy (Smith et al., 2012), and children with mixed seizure types (Hermann et al., 2016). Latent developmental trajectories have been identified in children with TLE (Wilson et al., 2012), in patterns of fMRI language activation (Berl et al., 2014), and presentations of MR abnormality in TLE (Bernhardt, Hong, Bernasconi, & Bernasconi, 2015). This approach may identify groups of patients with similar neurobehavioral profiles, provide a more accurate representation of the variability inherent within syndromic groups, and be related to clinical or neuroimaging data to clarify underlying neurobiology (Dabbs, Jones, Seidenberg, & Hermann, 2009).

Latent groups can be observed in regard to the behavioral comorbidities as well. Rayner, Jackson, and Wilson (2016b) identified two clinically distinct, symptom-based phenotypes of depression in people with focal epilepsy, namely a cognitive and somatic phenotype reflecting (Wilson

& Baxendale, 2014) different clusters of cognitive and vegetative symptoms associated with differential disruption of the underlying network in which the epilepsy principally resides (e.g., the cognitive control or affective network and their interactions (Wilson, 2011). In the short-term, this conceptual advance promises to improve the recognition and management of depression in people with epilepsy, while in the longer-term it may lead to insights into its pathogenesis and the development of individually-tailored treatments (Rayner et al., 2016a).

## CONCLUSION

The 50 years since the founding of the *INS* have seen many contributions to epilepsy care and research by clinical and experimental neuropsychology, just a few of which were touched on in this review. Progress can be marked by major shifts in thinking, or paradigm shifts altering clinical care, and we have seen our share in this field. Our progress has been substantial and often linked to advances in neurology, radiology, EEG, psychiatry, and other fields caring for people with epilepsy, so the collaborative nature of progress will continue to be key. Fifty years is the current lifespan of the *INS*, but it is but a brief epoch in the history of the epilepsies, and much remains to be done. With the continuing application of diverse sophisticated multimodal neuroimaging techniques (Chang et al., 2017) and increasingly innovative analytic approaches (Doucet et al., 2015; Vaessen et al., 2012), the relationship of neurobiological markers of cerebral integrity to cognition and cognitive outcomes will continue to strengthen our understanding of the intersection of cognition, behavior, brain structure, and epilepsy and its treatment.

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