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Paradigm Shifts in the Neuropsychology of Epilepsy

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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 brain mechanisms associated with a wide variety of cognitive and behavioral constructs. 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) features (Dodrill & Matthews, 1992). These and other efforts have informed our understanding of disease effects on brain development, aging and function. Finally, with the continuing development of diverse neuroimaging techniques, cognitive abnormalities and their relationship to a variety of neurobiological markers of cerebral integrity have strengthened our understanding of the intersection of cognition, brain structure, and epilepsy.

In this review, we focus on what we believe are particularly significant advances that have occurred in the intersection 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 discussed, will 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 lies ahead for clinical and research directions in the neuropsychology of epilepsy.

The neurobiology of cognitive disorders in epilepsy—breaking free from syndrome-specific pathophysiology?

The primary phenotyping of patients with epilepsy has been through the international classifications of the epilepsies which have evolved over the decades, with focal epilepsies considered in terms of their lobar site of origin, and neuropsychological investigations focused on presumed structure-function relationships such as executive function in frontal lobe epilepsy and of course memory in temporal lobe epilepsy (TLE). Temporal lobe epilepsy, the most common of the localization-related epilepsies, and its surgical treatment through anterior temporal lobectomy, the most frequently performed epilepsy surgery, have provided a unique window into the neurobiology of cognitive disorders in epilepsy given the care with which these patients are investigated prior to surgery and afterwards. Dating back to the 1960's and 1970's, the critical distinctions between declarative and procedural memory systems were demonstrated by Milner through study with HM (Milner, 1965) and the material-specific model of anterograde memory was developed and dominated thinking (Milner, 1972).

This model posited that if seizure onset originated from the left language dominant temporal lobe then verbal learning and memory would be adversely affected. Although somewhat less robust, if onset derived from the right nondominant temporal lobe, learning and memory for non-verbal material such as designs or faces would be affected. Non-memory cognitive abilities were presumed to be relatively unaffected because seizure onset and focal epileptiform abnormalities were restricted to the temporal lobe and its mesial structures among whose primary function was to encode new information into memory.

Studies slowly demonstrated that the cognitive and brain abnormalities of the focal epilepsies did not always respect pathophysiological boundaries. Given that memory impairments and/or asymmetries were a common clinical feature of TLE related to hippocampal neuronal loss and sclerosis, but these focal neuropsychological impairments were far from the sole consequences of the disorder and occurred against the backdrop of considerably more generalized cognitive abnormality, affecting not only memory, but also IQ, executive functions, language, sensorimotor, and other abilities (Oyegbile et al., 2004). Similarly, a core belief associated with the genetic generalized epilepsies (GGE) has been that attention and/or executive function are the primary associated cognitive consequences. This notion was also challenged by a recent meta-analysis of patients with GGE including juvenile myoclonic epilepsy, showing an adverse impact on all cognitive domains except for visuospatial abilities (Loughman, Bowden, & D'Souza, 2014) and, of particular note, there was not disproportionate impairment of executive function. Similarly, neuropsychological distinctions between focal epilepsy syndromes in children with epilepsy (e.g., temporal versus frontal lobe epilepsy) are far less crisp than believed, like due to the overriding impact of epilepsy on normal neurodevelopmental processes (Smith, 2016).

Although some have suggested that generalized neuropsychological impairment reflects inherent limitations of neuropsychological tests, neuroimaging studies have demonstrated similar distributed abnormalities in brain networks and association with disordered cognition. Imaging of the epilepsies has progressed rapidly and its impact has been profound. In one important early attempt to address this issue, Sisodiya and colleagues

(Sisodiya, Free, Fish, & Shorvon, 1995) devised an MRI postprocessing method that yielded multiple (n=80) indices reflecting volumes of cortical gray, white matter and subcortical structures, as well as metrics of abnormal asymmetries and other cortical features.

Compared to controls, an increased number of distributed abnormalities in “normal” clinical MRIs were documented in surgical patients with TLE and found to be associated with not only poorer surgical outcome (Sisodiya et al., 1997) but also adverse cognitive (memory) outcomes (S. A. Baxendale et al., 1999). From early efforts such as this, a steady stream of neuroimaging papers using diverse techniques documented the remarkable range of abnormalities extending outside the ipsilateral (to seizure onset) temporal lobe to ipsilateral extra-temporal regions, to contralateral hemisphere and subcortical structures and cerebellum (Keller & Roberts, 2008), including diffusely distributed cortical thinning (J. J. Lin et al., 2007; McDonald et al., 2008), and widespread abnormalities in white matter volumes and connectivity (Hermann et al., 2003; Seidenberg et al., 2005; Slinger, Sinke, Braun, & Otte, 2016). Early structure-function investigations documented relationships between hippocampal atrophy and memory (Lencz et al., 1992; Trenerry et al., 1993), while subsequent studies reported a wide range of brain- behavior links including associations between frontal abnormality with executive function (Keller, Baker, Downes, & Roberts, 2009).

Thus, the paradigm shift is that the landscape of cognitive abnormality is not driven solely by the location of the epilepsy and its related pathophysiology, but by the nature, range and severity of underlying distributed neurobiological abnormalities (Bell, Lin, Seidenberg, & Hermann, 2011; Hermann, Lin, Jones, & Seidenberg, 2009), the etiology of which remains to be clarified (Rayner, Jackson, & Wilson, 2016). That said, cognitive abilities depend on distributed neural networks and the degree to which these networks are impacted will be a path of investigation going forward (McDonald et al., 2014).

Pathways to comorbidities: Bidirectional relationships and their clinical implications

Substantial epidemiological and clinical research has demonstrated that epilepsy patients carry a significantly elevated burden of medical/somatic, psychiatric, and social disorders, in addition to cognitive difficulties (Tellez-Zenteno, Matijevic, & Wiebe, 2005; Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007). Although this literature has convincingly demonstrated the co-occurrence of these disorders with epilepsy, their temporal sequence has been less vigorously studied. The classic view has been that chronic epilepsy, including its recurrent clinical and subclinical seizures, persistent interictal EEG abnormalities, adverse effects of antiepilepsy drugs (AEDs), and psychosocial complexities of living with epilepsy, all serve to contribute to the development and progression of comorbid conditions.

A major disruption to this paradigm was the discovery of the so-called “bidirectional relationship” between epilepsy and cognitive, psychiatric, and social comorbidities in both pediatric and adult epilepsies (Hesdorffer, 2016). Psychiatric comorbidities have been the most widely investigated, and not only do they frequently appear prior to seizure onset, but may also serve as an important risk factor for subsequent epilepsy development. This bidirectional relationship has been reported for a variety of comorbid conditions including depression, suicidality, ASD, ADHD, psychosis, and schizophrenia (Lin, Mula, & Hermann,

2012). Not only are there shared susceptibilities between epilepsy and specific behavioral comorbidities, but of particular interest is evidence of co-aggregation of cognitive, behavioral, and even brain structural abnormalities in the siblings and parents of persons with epilepsy compared to general population controls (Alhusaini et al., 2015; Aronu & Iloeje, 2011; Badawy, Vogrin, Lai, & Cook, 2013; Chowdhury et al., 2014; Hesdorffer, Caplan, & Berg, 2012; Iqbal et al., 2015; Iqbal et al., 2009; Singhi, Bansal, Singhi, & Pershad, 1992; Tsai et al., 2013; Verrotti et al., 2013; Wandschneider et al., 2014; Wandschneider et al., 2010). These observations suggest the presence of distinct endophenotypes underlying epilepsy and some of its comorbidities, suggesting possible shared genetic mechanisms, although the influence of environmental factors remains to be clarified.

An important clinical inference associated with “bidirectionality” is that psychiatric, cognitive, learning or social comorbidities may be present at diagnosis in children and adults with new onset epilepsies. Indeed, adults and elders with new onset epilepsies display a pattern of mild diffuse cognitive impairment at diagnosis and prior to treatment with medications (Taylor et al., 2010; Witt & Helmstaedter, 2012; Witt et al., 2014), with an abnormal prospective 1 year and 5 year cognitive course that predominantly affects memory, executive function and psychomotor speed (Baker, Taylor, Aldenkamp et al., 2011; Taylor & Baker, 2010) (See Witt & Helmstaedter, 2015 for review). In children with new onset epilepsies, evident at or near the time of diagnosis, and even preceding the first recognized seizure, are elevated rates of behavioral problems including ADHD, depression and anxiety, early life histories of academic struggles and provision of special academic services, with a pattern of distributed cognitive anomalies (Pohlmann-Eden et al., 2015). These findings have critically important implications for clinical care as the imperative should be for neuropsychology to become more involved in the routine clinical care of persons with epilepsy, screening new onset cases for pertinent comorbidities in order to initiate timely treatment, and follow patients prospectively to monitor their progression (S. J. Wilson et al., 2015).

The bidirectional nature of epilepsy comorbidities has been an important paradigm shift, but caveats include: 1) similar bidirectional relationships have been reported for several chronic conditions including stroke, diabetes and cardiovascular disease, as well as a prodrome for dementia, suggesting a broader phenomenon that is not epilepsy-specific, 2) only a subset of persons with antecedent psychiatric disorders develop epilepsy, and similarly, only a subset of those with new onset epilepsy present with or develop a psychiatric or cognitive comorbidity early on, suggesting that this relationship reflects a unique phenotype, 3) especially in adults, the contribution of a life history of adverse lifestyle and health conditions to the risk of epilepsy and its comorbidities more generally remain to be characterized, and 4) the presence of a bidirectional relationship does not in and of itself imply shared causality – for this, biological mechanisms need to be identified.

Discovering quality of life: The concept, its quantification and applicability

Quality of life (QoL), reflected in the general wellbeing of individuals and societies, has become a core component in the quality of care in epilepsy. This came about through three

stages. First, prior to 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 intellectual assessment). Thus, “QoL” was characterized by a mix of diverse cognitive and personality measures representing a battery-type approach in order to characterize disease and treatment effects and patient status.

Second, an important trend developed to construct disease-specific measures that were meant to be particularly informative in the assessment, monitoring, and treatment of epilepsy patients—so-called “disease-specific” measures designed to assess specific issues associated with life with epilepsy. The most influential of the early epilepsy-specific measures 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). This had a major effect on the field, was translated and used internationally, and contributed to a “common language” for characterizing psychosocial complications.

The most recent approach has been the integration of formal HRQOL logic and methods into epilepsy care and research. Epilepsy surgery was again a prominent area for the initial development of HRQOL measures, including the Epilepsy Surgery Inventory-55 (Vickrey et al., 1995). This reflected a blend of generic items (Rand 36-Item Health Survey 1.0 (aka SF-36) supplemented by items assessing cognitive function, role limitations due to memory problems, health perceptions and overall assessment of quality of life. This approach was expanded in the Quality of Life in Epilepsy Inventory-89 items (QOLIE-89) (Devinsky et al., 1995), with subsequent short-forms of 31, and 10 items (Cramer et al., 1998). The long version was an expansion of the epilepsy-specific component of this mixed generic and disease-specific instrument, designed to be applicable to settings outside of epilepsy surgery with less severely affected epilepsy patients.

Also 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 outcomes, *seizure severity* had been ignored, and was found to be related to self-esteem, locus of control, and anxiety, while seizure frequency was not. Baker and colleagues additionally developed a patient-based HRQOL model for epilepsy including domains of physical, social and psychological function, as well as a battery approach to assess the various dimensions which included previously validated measures of anxiety, depression, happiness, overall mood, self-esteem, mastery, social satisfaction and general health. From these earlier efforts, many additional measures have followed, including those for use with non-English speaking epilepsy populations or specific patient groups. The NEWQOL is one such example developed for newly diagnosed epilepsy patients by the Liverpool group (Abetz, Jacoby, Baker, & McNulty, 2000).

Research into psychological and social adjustment has complemented this HRQOL work, with the Melbourne group demonstrating that the diagnosis of a first seizure gives rise to a process of losing and restoring perceived control. Two psychological adjustment trajectories were identified, which 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). Overall, the notion of health-related quality of life has been institutionalized into epilepsy care and research.

Outcomes of epilepsy surgery: Challenging conventional wisdom

While 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), the 1980's witnessed the beginning of an explosion of interest in epilepsy surgery. Early on epilepsy surgery was considered a final treatment option following years of failed medication management and devastating psychosocial complications. But growing interest in epilepsy surgery and the proliferation of epilepsy surgery centers worldwide led to two influential international symposiums—the Palm Desert Workshops on Epilepsy Surgery (Engel, 1993) which were transformative in fueling critical thinking regarding including patient evaluation and selection, surgical treatments, outcome assessments, and the consideration of epilepsy surgery as a treatment option to consider earlier in the course of epilepsy. Neuropsychology's close involvement with epilepsy surgery led to several major changes in thinking and practice.

Cognitive outcomes—A primary concern regarding anterior temporal lobectomy with resection of mesial structures was the risk of significant post-operative memory decline/ amnesia (Milner, 1958). Neuropsychological practice was therefore dominated by 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 as the prominent indicator of whether the contralateral temporal lobe had sufficient functional capacity to sustain memory function post-operatively, and (3) confirmation of this assumption 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 the degree 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; Sass et al., 1992; Sass et al., 1990). Second, advances in MR imaging allowed noninvasive quantification of hippocampal volumes which could then be related to preoperative memory performance (Lencz et al., 1992; Trenerry et al., 1993), also allowing examination of hippocampal-memory relationships both ipsilateral and contralateral to the side of eventual surgery. These contributions demonstrated clear relationships between hippocampal pathology (or lack thereof) with the status of preoperative memory and Wada test performance. Third, a logical extension of this work was examination of postoperative memory outcomes as a function of markers of ipsilateral hippocampal integrity reflected in

cell counts, quantitative MRI, or adequacy of preoperative memory function. This work demonstrated that resection of less diseased/more functional hippocampus resulted in significant memory decline (Hermann, Wyler, Somes, Berry, & Dohan, 1992; Sass et al., 1994).

This changing paradigm was crystallized in a review by Chelune (1995) in which he suggested that the *functional integrity* of the to-be-resected hippocampus, as reflected by less hippocampal atrophy, higher 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 to assessment techniques such as preoperative memory assessment via fMRI in which the strongest predictor of memory decline following ATL is ipsilateral posterior hippocampus activation (Bonelli et al., 2010), and extension to other cognitive domains. Lastly, the material specific model of memory has been unable to explain the many failures to link right hippocampal resection to “non-verbal” visual memory declines. In a major contribution, Saling (2009) suggested that task-specificity, rather than material-specificity, was the more relevant factor in verbal memory outcomes, as it distinguished medial versus lateral specialization (or intra-temporal organization of memory) within the temporal lobe.

Alternative surgical techniques and their impact—Given the implications of ipsilateral functional integrity and concern regarding other iatrogenic surgery effects, multiple surgical approaches were pursued to minimize cognitive morbidity. This is a topic too large to review here, but among the developments was selective amygdalohippocampectomy, which aided to maximally preserve the cortical temporal lobe zone, and restricting surgical resection to the hippocampus (Helmstaedter, Elger, Hufnagel, Zentner, & Schramm, 1996). Unfortunately, the magnitude of improved cognitive outcomes typically was no better than standard cortical resection, presumably due to collateral white matter damage sustained in the surgeon’s access to the medial temporal lobe structures (Kuang, Yang, Gu, Kong, & Cheng, 2014). Over time it became clearer that focusing resection on diseased hippocampus and avoiding collateral white matter involvement resulted in considerably improved memory outcomes. Helmstaedter (2013) has reviewed the cognitive outcomes of various surgical procedures.

From anterograde to semantic memory systems—Also changing over this time was a greater appreciation of the effects of focal epilepsy, particularly left temporal lobe epilepsy, on semantic memory. Multiple reports suggested a robust relationship between confrontation naming ability and seizure onset laterality, oftentimes exceeding the relationship with verbal learning and memory (Busch, Frazier, Iampietro, Chapin, & Kubu, 2009). Further, slightly more than 40% of left TLE patients undergoing surgical resection may experience naming decline while only 5% of right TLE demonstrated decline (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. Interestingly, left TLE patients that display impaired confrontation naming are generally able to recognizing

famous faces and objects (Drane et al., 2008), whereas right TLE is often associated with recognition impairment which is thought to result from impaired ventral visual processing stream reflecting a mild visual agnosia. All this clearly suggests that assessment of visual naming does not capture the full impact of epilepsy and epilepsy surgery on the semantic memory network (Drane et al., 2008).

The plasticity of the epileptic brain—Throughout the 20th century, the primary method for establishing cerebral language dominance prior to epilepsy surgery was through use of 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 prior to 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). But as Wada techniques became increasingly refined, they also demonstrated that exclusive right hemisphere representation is rare and that language reorganization typically exists on a continuum (Loring, Meador, Lee, Murro, et al., 1990) which is now commonly 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 specific clinical factors including age of injury onset, region of onset, and magnitude of injury (Stewart et al., 2014) with a language shift offering in the absence of a shift of verbal learning and memory (Loring, Meador, Lee, Flanigin, et al., 1990; Wood, Saling, O’Shea, Jackson, & Berkovic, 1999).

Significantly decreasing the use of Wada testing across many epilepsy centers has been the development and validity of numerous language paradigms that 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. What has not yet been satisfactorily developed, in fMRI memory, is a reliable replacement to Wada memory testing or standardized replacement that is consistently used across centers.

QoL outcomes—Key in the development of epilepsy surgery has been a desire to improve the life of people with epilepsy, a theme that occurs repeatedly in the literature. In fact, in the early days of the University of Illinois surgical program, a pioneering electroencephalography (Fred Gibbs) convinced a reluctant neurosurgeon (Percival Bailey) to operate on the basis of EEG only, because he knew that otherwise the patients’ pervasively compromised quality of life would persist (Hermann & Stone, 1989). But it is after all a somewhat naïve assumption that a patient with significantly compromised cognitive, psychiatric and social status would suddenly improve their life situation due to surgical intervention without broader rehabilitation efforts. The more sober of epilepsy surgery clinicians would state that, “What comes out of surgery is what went in”, the

implication being that broader efforts need to be devoted to imparting new skills in the context of epilepsy surgery.

Here a focus on the process of psychosocial change after surgery by the Melbourne group identified that a complex set of psychological and social changes need to occur after surgery in order for the patient to truly benefit from seizure freedom (Bladin, 1992; Wilson, Bladin, & Saling, 2001). This process, driven by a change in patient identity as they learned to 'become well', gives rise to a consistent set of psychological and social features that constituted a syndrome, termed the 'burden of normality'. This work has shown that while seizure freedom may be necessary for improved QOL after surgery, it is not sufficient, with patients and families also requiring post-operative rehabilitation and psychosocial support as they adjust to 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. Considerable work has been done to identify predictors of this negative outcome, with a range of factors, including a pre-operative psychiatric history and smaller contralateral hippocampal volume, 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, and the FDA has issued guidance that neuropsychological testing should be included for children. The first systematic characterization of different AED profiles was by Dodrill and Troupin (1977) who reported a more favorable outcome associated with carbamazepine compared to phenytoin, although this study also demonstrated some of the inherent problem associated with trial design since comparable drug levels were not used, and upon appropriate reanalysis, the differential cognitive drug effects were no longer present.

The most influential paper reporting cognitive AED effects on clinical practice was the demonstration that phenobarbital used for seizure prophylaxis after a febrile seizure was associated with FSIQs that were approximately $\frac{1}{2}$ SD lower than placebo treated children (Farwell et al., 1990). Not only were these difference present during treatment, but they also persisted following phenobarbital discontinuation indicating cumulative treatment effects from which the children were unable to catch up (Sulzbacher, Farwell, Temkin, Lu, & Hirtz, 1999). These reports, combined with reports of no therapeutic benefit in decreasing subsequent epilepsy, 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 are at times difficult to apply on an individual patient basis and that oftentimes, studies are 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 literature on cognitive side effects of AEDs have been

published, although information on the more recently introduced medications are not included (Loring, Marino, & Meador, 2007; Vermeulen & Aldenkamp, 1995).

Even when neuropsychological outcomes are not the primary endpoint in clinical trials, they are increasingly being used to characterize overall treatment “effectiveness” rather than relying solely on 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 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 on memory or naming depending on the location of stimulation (Loring, Kapur, Meador, & Morrell, 2015).

Where is the neuropsychology of epilepsy headed 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 and conditions.

Changes in assessment paradigms

From a strictly clinical perspective, we anticipate that in the US it will be more difficult to obtain approval to conduct comprehensive neuropsychological evaluations outside the context of surgical evaluation, although changes in health insurance coverage are always 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 issues, especially in new onset cases, and cognitive screening will become a routine part of “Brain Health” 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 with the NIH Cognitive Toolbox or the NIH PROMIS (Nowinski et al., 2016), and hopefully more innovative approaches such as using virtual reality approaches designed to maximize ecological validity of constructs. While some may see this as a threat to clinical neuropsychological practice, we view this as a way to characterize cognitive and behavioral comorbidities on more of a population basis rather than by selective referral, and patients meeting various thresholds of cognitive impairment will continue to require more comprehensive evaluation for effective clinical management.

Moving from characterization to interventions

The neuropsychology of epilepsy literature is largely one of characterization of disease effects with finer and more detailed re-characterization of the possible complications of epilepsy (depression, anxiety, cognitive abnormalities, social interaction problems). There has been increasing emphasis on screening and early identification of these problems, but critical are systematic intervention trials to improve life status. Unfortunately, there are few

non-pharmacological intervention that have been demonstrated to be successful in epilepsy patients (Adams et al., 2017). These are slowly beginning to appear and will increase in the future (Jackson, Makin, & Baker, 2015; Ramaratnam, Baker, & Goldstein, 2008) and will be critical to improving patient life outcomes.

New appreciation of an old technology: EEG and epileptogenic spikes

Investigation of the influence of epileptogenic spikes and other abnormal waveforms dates to Shwab's (1939) early investigations that appeared not long after development of the EEG and its application to epilepsy (Fastenau, 2011). Although elegantly demonstrated in animal studies, the contribution of EEG abnormalities on real time cognition in humans has been murkier. This likely reflects a combination of factors including differences in discharge form (spike and wave vs. sharp waves), density of EEG abnormalities, neuropsychological factors of test sensitivity and practice effects, and research design considerations that contrast periods of active discharges to quiescent periods in the same subject. It is clear that the condition of transient cognitive impairment associated with subclinical seizures/short non-convulsive seizures may affect cognition (Aldenkamp, Arends, Verspeek, & Berting, 2004). Although a continuum between short non-convulsive seizures and interictal exists, unknown are the parameters that might be necessary to influence cognition. However, this has considerable clinical importance, both for the preoperative evaluation of patients that may have frequent discharges as well as treatment effects in which, in contrast to contemporary practice, a decision might be made to initiate AED based on interictal EEG patterns rather than seizures themselves (Dinkelacker, Dupont, & Salmson, 2016).

The effects of focal EEG discharges from the temporal lobes has been repeated demonstrated in the condition of transient epileptic amnesia, in which relatively isolated memory impairment similar to transient global amnesia present, but which is thought to reflect due to focal seizure in part due to its responsiveness to AED initiation. With the aging of the world population this syndrome we suspect that increasing interest in the so-called transient amnesic syndromes including transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment will be an increased area of interest (Butler & Zeman, 2008).

Increasing development of new measures, terminology and classification

Our colleagues in neurology, electroencephalography, surgery, radiology and other fields have been rapidly developing and advancing impressive new technology to apply to epilepsy and its comorbidities. Neuropsychology has the dubious distinction of advancing via new versions of established general tests (Loring & Bauer, 2010). But colleagues are making new inroads into assessment of language function in epilepsy (Hamberger & Cole, 2011), category specific "naming" (Drane et al., 2008), social function (theory of mind) (Giovagnoli, 2014) and other areas which have an underlying neurobiological signal and which are clearly relevant to epilepsy care and deserve consideration in routine assessments. We still lack a common language of assessment internationally, very few common international epilepsy specific measures with the exception of quality of life and mood, we have no cognitive taxonomy such as used in the aging world. Consider what the status of

epilepsy would look like were there no international classification system for epilepsy seizures and syndromes. Hopefully these will be areas of interest.

Increasing interest in neurodegenerative proteins

The older epilepsy literature referred to the dementia-like end state of chronic epilepsy. In fact, the early epilepsy colonies frequently contained specific buildings for epilepsy patients with brittle psychiatric disorders and dementia. The contemporary epilepsy literature has been interested in neuroimaging and cognitive biomarkers of “progressive disease”, although these issues continue to remain controversial. Assessing the proteins of neurodegeneration including tau (Sen et al., 2007; Tai et al., 2016; Thom et al., 2011) and beta-amyloid (Joutsa et al., In Press; Mackenzie & Miller, 1994) are really just beginning, and we expect that there will be more work examining the presence and distribution of neurodegenerative proteins such as beta amyloid and tau and their relationship to cognition and cognitive change in epilepsy.

Transitioning from clinical seizure features to modifiable risk factors

The epilepsy-neuropsychology literature dates back to the early twentieth century and as we have noted, has characterized in detail the cognitive morbidity associated with the epilepsies and its association with the cause, course, and treatment of the disorder. In the general neuropsychology literature, a wide range of lifestyle, health, and social factors have been shown to be associated with accelerated cognitive aging and dementia in the general population, factors that are rarely examined in relation to cognition in epilepsy, an unfortunate omission as these and other related factors are generally viewed as potentially modifiable risk factors. Work is beginning to appear on factors such as exercise, obesity (Baxendale et al., 2015; Hamed, 2015), vascular risk (Hamed, 2015) and metabolic abnormalities in epilepsy—some related to cognitive status (Baxendale et al., 2015). These are important developments as recent population based investigation has shown atrophy of cerebral white- matter volume to be associated 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). Relatedly, population based investigations have shown elevated vascular risk factors that could assist in explaining the high risk of cerebral and cardiac vascular disease in epilepsy patients (e.g., hyperlipidemia) (Harnod, Chen, Li, Sung, & Kao, 2014), which may be due in part to untoward antiepileptic medications (Brodie et al., 2013). We suspect this will be an important new direction in the field with emphasis on maintenance and improvement of brain and cognitive health.

Conclusion

The 50 years since the founding of the INS have seen many contributions to epilepsy care and research by clinical and experimental neuropsychology, a few of which were touched on in this review. Progress can be marked by major shifts in thinking, or paradigm shifts, and we have seen our share in this field. Our progress has been substantial and often linked to advances in neurology, radiology, electroencephalography, psychiatry and other fields caring for people with epilepsy—so the collaborative nature of progress will continue to be key.

Fifty years is the lifespan of the INS to date, but it is but a brief epoch in the history of the epilepsies, and much remains to be done.

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