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**Editor’s Corner**

The spring edition of the NAN Bulletin for 2014 focuses on epilepsy. Neuropsychologists have a longstanding history of contributing to the understanding of epilepsy through clinical care and research endeavors. As we build upon our past, we also strive to continually improve our methods of assessment and intervention so that we may improve outcomes of individuals with epilepsy. To that end, we have assembled a group of authors with a wealth of knowledge in epilepsy and whose work has influenced many of us who serve individuals with epilepsy.

In addition, our Student Section focuses on board certification in neuropsychology. Representatives from the American Board of Clinical Neuropsychology (ABCN) and American Board of Professional Neuropsychology (ABN) have provided descriptions of their respective boards, which should be especially informative for interns, fellows, and practicing neuropsychologists who are looking ahead to board certification.

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American Board of Professional Neuropsychology: An Update-2014

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Abstract
This article is an update on the status of the American Board of Professional Neuropsychology (ABN). ABN is a free-standing post-doctoral level Diplomate granting certification board established in 1982 and reorganized in 1991. The mission of ABN is to establish and maintain professional standards for expertise in the practice of clinical neuropsychology. The acronym for the American Board of Professional Neuropsychology was changed from ABPN to ABN in 2008.

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While there had been four previous published descriptions of the American Board of Professional Neuropsychology (Bennett, Horton & Elliott, 1999, Elliott & Horton, 1994, 1995, Horton, Crown & Reynolds, 2001), including two articles published in the Bulletin of the National Academy of Neuropsychology, an update is warranted and has been requested by the editors of the Bulletin of the National Academy of Neuropsychology.

The ABN’s primary mission is the establishment and continual reassessment of professional standards for the pursuit of excellence in the practice of professional neuropsychology. This differs from the goals/tasks of the many states and provinces which certify or license psychologists and identify practitioners at a minimum level of competence. The ABN, through its credentialing process offers to the public and individuals who would have a need for professional neuropsychological services, a means whereby well qualified professional neuropsychologists can be identified.

Brief Background
In order to understand the current status of the American Board of Professional Neuropsychology, it is helpful to understand the origin of the board. Two major early influences are considered, the qualifications of original founders and the broader movement toward professional credentialing.

In 1982, the initial Diplomates for ABN were a group of clinical neuropsychologists who held the Diplomate from the American Board of Professional Psychology (ABPP) in psychology specialties other than neuropsychology. The initial ABN examination process was developed by individuals who already held ABPP Diplomate status as well as ABN Diplomate in Professional Neuropsychology.

The original examination committee developed the ABN examination to be similar to that of medical specialties and the ABPP examination.

An additional major influence on ABN was the broader movement to credential healthcare workers. In the 1970s the Department of Health, Education and Welfare (HEW) found that many healthcare workers, despite having degrees and completing academic training programs, were nonetheless incompetent to perform their duties as healthcare workers. In order to address this major problem in healthcare, a movement was started to create certification procedures specific to types of healthcare workers which were based on an objective demonstration of competence. The HEW healthcare credentialing movement required an objective examination that was based on a job analysis (Henderson, 1996), a survey of healthcare providers in specific areas stressing the importance of various areas of knowledge, the frequency this area of knowledge was used for patient care, and the potential for harm of a healthcare worker not having the specified areas of knowledge. ABN followed these certification procedures in the development of its examination process. For example, ABN transitioned from an essay-based written examination to a rigorously developed multiple choice examination implemented in 2004. (For details see www.ABN-Board.com).

Application Requirements
There are two application options available for the ABN certification candidate-- the Standard application and the Senior Option application. The Senior Option was instituted in 2008 to encourage those with a minimum of 15 years of experience and expertise in the field of neuropsychology to pursue Diplomate status. This option recognizes that many professionals who have worked in the field for many years and may not have completed a formal postdoctoral fellowship. The two application options are very similar and follow essentially the same rules. The essential difference between the Standard and Senior application is allowance for differences in training that were available in the past. The costs involved in the examination process are listed on the ABN website. The Senior Option gives a 50% reduction in fees. Neuropsychologists who already belong to a neuropsychology specialty board that meets or exceeds the requirements proposed by the APA for recognition of specialty boards are eligible for the ABN Diplomate. (For details see www.ABN-Board.com).
The multi-step application process will allow applicants to have their backgrounds and competencies critically evaluated early in the process.

The Initial Application
During this application phase, training and course work are evaluated to ensure that the applicant has acquired the required appropriate training. This training can be fulfilled in a formal post-doctoral program or in less structured programming, as long as the individual can document areas and adequacy of training. The ABN application coordinator answers questions regarding the application process (see www.ABN-Board.com for details and contact information). The applicant handbook (available on the above website) contains a detailed description of the entire ABN Diplomate evaluation process and a list of suggested books to read when preparing for the examination. ABN also sponsors a workshop on the examination process every year at the NAN Convention.

The Written Multiple Choice Examination
After acceptance of the application, the applicant will be required to take the 100- question written examination. The ABN multiple choice examination is intended to assess general knowledge in clinical neuropsychology. Test questions were developed in multiple-choice format by board certified neuropsychologists who were also board examiners trained in question writing based on measurement and assessment in education (Reynolds, Livingston & Wilson, 2006).

The written multiple choice examination is based on a job analysis and survey of board certified neuropsychologists consistent with recommended practices for developing health care provider certification procedures. The multiple choice exam is also based on the training recommendations of the Houston Conference guidelines (Hanney, et al., 1998).

The Work Samples
After passing the written multiple choice examination, the applicant has one year to submit two work samples for review and approval by the Chairperson of the Work Sample Examination Committee. The work samples provide the Examination Committee with further data to evaluate the competencies of the candidate. Materials submitted from professional activities should reflect current clinical practice activities no more than two years old. Based on objective scoring criteria, the work samples are scored by trained work sample examiners. (See Applicant Handbook for details).

The Oral Examination
The purpose of the ABN Oral Examination is to critically evaluate the candidate’s current knowledge base and ability to conceptualize and apply clinical and ethical principles. The candidate will be treated as a respected colleague whose general knowledge, experience, and work sample have already passed very careful scrutiny.

Standardized scoring criteria are utilized to assess for relevant points being considered in the response. The examiner primarily utilizes general, open-ended questions to provide opportunity for necessary breadth of consideration in the response. The examination will be focused on the examinee’s areas of practice and expertise. The examination will provide the candidate with an opportunity to demonstrate his or her clinical expertise. The examiner will be prepared to make special efforts to reduce the candidate’s understandable anxiety.

Appeals Process
In an effort to ensure a fair and impartial examination, the Board provides an appeals process for any candidate who believes that his or her examination was not conducted in a manner consistent with the ABN examination policies. A request for an appeals review should be submitted in writing within thirty (30) days of the initial notice of No Pass. The candidate’s request shall include a statement of the specific factors or conditions considered by the candidate as having interfered with a fair and impartial evaluation. The candidate’s written appeal will be reviewed by an Appeals Committee consisting of three members of the Board, not to include members of the candidate’s Examination Committee. The Appeals Committee may review documents and request additional written information. Its members will determine whether or not the examination was conducted in a manner consistent with the ABN policies.

ABN Recognition & Advocacy
The ABN Board of Directors and membership at large promote the ABN Credential and services to the public, practitioners, students and the field, as well as consumers. In 2002, the ABN became recognized by the National Register of Health Service Providers in Psychology. In 2008, the ABN became affiliated with the peer-refereed journal Applied Neuropsychology. In 2011, the official journal of The ABN was expanded to include two journals, Applied Neuropsychology - Adult and Applied Neuropsychology - Child.

Practitioners are aware that states often do not recognize specialties, but rather grant a general license to practice psychology. This practice, however, is evolving. In March 2008, ABN was successful in being recognized by the state of Florida as a specialty certification board. Other states where ABN has been recognized include Texas and Louisiana. In 2013 the Federal Aviation Administration (FAA) recognized ABN members as qualified to conduct pilot and flight crew evaluations. In 2013, ABN was recognized by the Commission for the Recognition of Specialties and Proficiencies in Professional Psychology (CRSPPP) of the American Psychological Association (APA) as a certification body which allows ABN members of APA to list the ABN credential in the APA directory.

ABN is a member participant of the Inter-Organizational Practice Committee (IOPC). As such, ABN works with similar organizations as part of a supportive network dedicated to the advancement of the field of neuropsychology. The IOPC members collaborate on a variety of projects. An online tool kit is available to all practitioners (http://neuropsychologytoolkit.com/). ABN additionally maintains a member-only online resource for similar information as well as dissemination of information of relevance to members.

Invitation
ABN encourages all neuropsychology practitioners to pursue board certification with ABN or other well-recognized boards as may correspond to the practitioner’s needs, opportunities and resources. ABN’s official web site is www.ABN-Board.com, from which its Board of Directors, Committee Chairs and organizational initiatives can be accessed.
Arthur MacNeill Horton, Jr. received his Ed.D. Degree from the University of Virginia and holds ABPP Diplomates in both Clinical Psychology and Behavioral Psychology and an ABN Diplomate in Neuropsychology and is the author/editor of 15 books. He is a past-president of the American Board of Professional Neuropsychology (ABN), the National Academy of Neuropsychology (NAN) and the Maryland Psychological Association (MPA). Currently, Dr. Horton is in private practice at Psych Associates of Maryland in Towson, Columbia and Bethesda, Maryland and Editor in Chief of both APPLIED NEUROPSYCHOLOGY-ADULT and APPLIED NEUROPSYCHOLOGY-CHILD.

Dr. Elliott maintains an active practice in Los Angeles (Aerospace Health Institute) and specializes in aviation related assessments and consultation. Dr. Elliott is board certified in clinical neuropsychology by both the American Board of Clinical Neuropsychology and the American Board of Professional Neuropsychology (ABN). Dr. Elliott is past-president of the National Academy of Neuropsychology and ABN.

References


The American Board of Clinical Neuropsychology (ABCN) was incorporated in 1981 and has examined and board certified over 900 clinical neuropsychologists, with this number likely to exceed 1000 by the end of 2014. Depending on how one counts clinical neuropsychologists, this currently represents approximately 25% of potential practitioners.

Board certification through ABCN has been modeled on board certification for specialties in medicine and is easily identified as the desired credential for specialty practice. ABCN is one of 14 member boards of its umbrella board, ABPP just as 22 medical specialty boards are members of an umbrella board in medicine, the American Board of Medical Specialties (ABMS). The training model leading to board certification in clinical neuropsychology can be found in the Houston Conference policy statement (http://www.theaacn.org/position_papers/houston_conference.pdf) and includes completion of: 1) a doctoral program in applied psychology, 2) an internship program specializing in clinical neuropsychology, and 3) a two year postdoctoral residency in Clinical neuropsychology (Hannay et al., 1998). Candidates then submit their credentials for review, take a written examination in clinical neuropsychology, and undergo oral examination related to their clinical knowledge and practice.

Application materials and information regarding specialty board certification can be found on the ABPP website: www.abpp.org, and the ABCN website: www.theabcn.org. The American Academy of Clinical Neuropsychology (AACN) is a member organization which supports the board certification process and provides many educational materials, activities, and public documents relating to the practice of clinical neuropsychology: www.theaacn.org. The website also includes information about the annual AACN meeting which focuses on multiple workshops both at the basic and advanced levels of preparing for examination and maintaining specialty competence in clinical neuropsychology. Students can become affiliates of AACN for a nominal fee which includes a subscription to The Clinical Neuropsychologist and reduced fees for the annual meeting and workshop offerings. Students are also strongly encouraged to attend the annual AACN meeting which has many student-related activities in addition to excellent educational offerings. The AACN website includes a member directory where students can readily identify ABCN board certified specialists in their geographic area.

Students should be aware that ABPP provides an early application process for students wherein they can submit and maintain their credentials for a one-time fee of $25.00. This is a considerable saving over the standard $125.00 board examination application fee. More information on this can be found on the ABPP website. Students should also be aware that in addition to examination for general specialty competence in clinical neuropsychology, ABCN has also established subspecialty certification in Pediatric Neuropsychology, a certificate for which can be obtained in addition to the board certification credential. A Pediatric Specialty Interest Group (Peds SIG) has been formed under AACN to attend to the concerns of clinical neuropsychologists practicing with children. Students are welcome to attend the Peds SIG meetings which are part of the annual meeting of AACN.

The ABCN examination is designed to provide a standard by which competence to practice clinical neuropsychology is judged. It is intended not just as a measure of knowledge, but also as a tool to determine the effectiveness of application of neuropsychological principles in the clinical setting and the promotion of patient welfare. Students who prepare for and take the examination can be assured that they have met the highest quality standards for practice in their profession.

After an initial credentials review, a candidate has seven years to complete the board certification process. Candidates have three opportunities to pass the written examination, which consists of 125 multiple-choice questions and is administered four times per year at the same local exam stations as for the national licensing exam. The written examination is continuously updated and addresses the knowledge base and skills set forth in the integrated guidelines for education and training in clinical neuropsychology established at the Houston Conference on Specialty Education and Training in Clinical Neuropsychology in 1997 (Hannay et al., 1998). Candidates then have unlimited opportunities to submit and have their practice sample accepted, and three opportunities to pass the last stage, the oral examination which is held twice annually at the University of Illinois at Chicago. Candidates who do not pass the final opportunity of either the written or oral examination may reapply and begin the process again. An appeals process is in place for candidates who feel that their practice samples have not been adequately or fairly evaluated or that their oral examination did not conform to procedural standards.

The AACN was established in 1996 (Ivnik, Haaland, & Bieliauskas, 2000), held its first annual national meeting in Minneapolis in 2003, and has held annual meetings ever since. AACN intends for its meeting to become a leading outlet of continuing education for all clinical neuropsychologists. AACN also has engaged in other activities intended to promote both the board certification process and the specialty of clinical neuropsychology. When preparing for examination for board certification, AACN specifically supports a number of student activities and resources which can be found at the Study Materials link on the AACN website and which are summarized in the Resource Guide for ABCN Examination: http://www.theaacn.org/documents/aacn_abcn%20resource%20support%20guide_8.2013.pdf. For example, information for students can be found concerning “BRAIN” (Be Ready for ABPP in Neuropsychology), which is both a national study group and a repository for study materials on the practice of clinical neuropsychology. There are also several books available to aid in preparing for examination including Board Certification in Clinical...
Neuropsychology: A Guide to Becoming ABPP/ABCN Certified Without Sacrificing Your Sanity and The Clinical Neuropsychology Study Guide and Board Review, both which are published by Oxford Press. In addition AACN provides a mentorship program where candidates for examination can receive individual help from board certified clinical neuropsychologists. AACN also publishes position papers regarding important issues in clinical neuropsychology and has adopted The Clinical Neuropsychologist as its official journal.

AACN has clearly established itself as the largest and most rapidly growing membership organization of board-certified specialists in clinical neuropsychology. ABCN and AACN are proud of their history, tradition, and commitment to the profession's highest standards, and look forward to the continuing development and refinement of the board certification process and promotion of the specialty of clinical neuropsychology.

Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>1981</td>
<td>Division 40/INS Task Force members identify need for board certification in clinical neuropsychology</td>
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<tr>
<td>1981</td>
<td>ABCN incorporated in Minnesota</td>
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<tr>
<td>1983</td>
<td>First set of examinations completed</td>
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<tr>
<td>1983</td>
<td>Formal affiliation between ABCN and ABPP established</td>
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<tr>
<td>1984</td>
<td>First ABCN/ABPP diplomates awarded</td>
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<tr>
<td>1988</td>
<td>ABCN bylaws revised to create membership organization, institute dues collection, and clarify rights and requirements for members</td>
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<tr>
<td>1989</td>
<td>ABCN designated Specialty Council in Clinical Neuropsychology by ABPP</td>
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<tr>
<td>1993</td>
<td>Written examination formally instituted</td>
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<tr>
<td>1994</td>
<td>ABCN policies and procedures updated</td>
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<tr>
<td>1996</td>
<td>AACN established</td>
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<tr>
<td>1999</td>
<td>First AACN position paper published</td>
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<td>2001</td>
<td>AACN publishes written guide to examination process</td>
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<tr>
<td>2002</td>
<td>AACN establishes mentoring program to promote board certification</td>
</tr>
<tr>
<td>2002</td>
<td>ABCN affirms intent to incorporate Houston Conference guidelines into board certification process</td>
</tr>
<tr>
<td>2002</td>
<td>Written examination updated to reflect Houston Conference guidelines</td>
</tr>
<tr>
<td>2003</td>
<td>First annual AACN national meeting held in Minneapolis</td>
</tr>
<tr>
<td>2003</td>
<td>The Clinical Neuropsychologist established as official journal of AACN</td>
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<tr>
<td>2004</td>
<td>500th ABCN diplomate awarded</td>
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<tr>
<td>2014</td>
<td>1000th ABCN diplomate awarded</td>
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Linas Bieliauskas, Ph.D., is professor in the Departments of Psychiatry and Psychology at the University of Michigan, Training Director of the Neuropsychology Section, and staff psychologist at the Ann Arbor Veterans Affairs Medical Center. He is board certified through the American Board of Professional Psychology (ABPP) in Clinical Psychology and Clinical Neuropsychology and is a fellow of the Divisions of Clinical Health Psychology (38) and Clinical Neuropsychology (40) of the American Psychological Association (APA). He is past president of the International Neuropsychological Society and the Division of Clinical Neuropsychology (40) of APA, and is the Executive Director for the American Board of Clinical Neuropsychology and the American Academy of Clinical Neuropsychology. Dr. Bieliauskas is also senior editor for the journal Aging, Neuropsychology, and Cognition and editor for the book series Studies on Neuropsychology, Neurology and Cognition for the publisher Taylor and Francis. His research interests include cognitive, functional, and affective changes due to normal and abnormal aging, and cognitive and personality changes in chronic disease.

References


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Synopsis and Commentary on “Diminished Default Mode Network Recruitment of the Hippocampus and Parahippocampus in Temporal Lobe Epilepsy” from Journal of Neurosurgery

(James et al., 2013)

Use of Resting-state Functional Magnetic Resonance Imaging to Model Brain Networks in Epilepsy: Synopsis and Relevance to Clinical Neuropsychologists

G. Andrew James, Ph.D.; Jeffrey G. Ojemann, M.D.; Robert E. Gross, M.D., Ph.D.; and Daniel L. Drane, Ph.D.

Introduction
Over the past two decades, functional magnetic resonance imaging (fMRI) has been used to extensively map brain regions underlying cognition (Cabeza, et al. 1997; Laird, et al. 2005). Recent advances in neuroimaging statistical methods have allowed us to study how these task-related brain regions are integrated into larger networks subserving cognition. These functional connectivity methods have shown that task-related brain networks also have stable neural representations during wakeful rest (Beckmann, et al. 2005; Smith, et al. 2009). This finding has led to an increasingly popular paradigm known as resting-state fMRI (rs-fMRI) in which participants undergo fMRI for 7-10 minutes in the absence of an overt task. rs-fMRI has grown in popularity because it allows brain network organization to be evaluated at a basal state without the confounding influences of task difficulty or differences in experimental design (James, et al. 2009). For example, a motor task would require greater effort from a stroke survivor with partial hemiparesis than from a healthy control participant; this increased effort could confound comparisons of motor network organization across participants. Conversely, rs-fMRI requires no overt task and thus comparable effort between participants.

Functional Connectivity
Task-based fMRI paradigms are traditionally analyzed by assessing changes in magnitude of brain activity across task conditions (Cox 1996; Friston, et al. 1995). These approaches cannot be used for rs-fMRI due to the lack of overt tasks. Instead, rs-fMRI analyses rely upon a class of methods known as functional connectivity analyses, which examine the intrinsic fluctuations in regional brain activity over time. Regions with strongly correlated activity over time are posited to belong to the same functional brain network. Several methods have been developed for assessing functional connectivity. The least computationally intense approach is seed mapping, which calculates the bivariate correlation in activity between a target “seed” region and all other brain regions (Liu, et al. 1999). This approach identifies regions that share variance with the seed region, but cannot infer if they are part of a single network or multiple networks. Independent component analysis is a more complex signal-processing approach that identifies sources of shared spatiotemporal variance across brain regions – thus directly identifying networks with unique activity timecourses (McKeown, et al. 1998). Finally, graph theory is an approach that assesses the role of nodes (brain regions) within an existing network – for example, if a region serves as a “hub” within a network (with high correlation to all other regions) or is more tangential (primarily communicating with one or two other regions within the network) (Bullmore and Sporns 2009).

Default Mode Network
The default mode network (DMN) is a brain network characterized by greater activity during rest than task (Raichle, et al. 2001). It has been termed the “default mode” network because it consistently shows greater activity during rest for a broad range of tasks including motor execution, visual perception, and working memory. The DMN has a central “hub” of the posterior cingulate cortex with recruitment of the ventromedial prefrontal cortex, bilateral inferior parietal lobules, bilateral dorsolateral frontal cortices, and bilateral hippocampi and parahippocampal gyri. Based upon the recruitment of these regions, the DMN has been proposed to assist in memory consolidation, task engagement, and response preparation.

Influence of epilepsy upon DMN connectivity. The impact of temporal lobe epilepsy (TLE) upon interictal (i.e., between seizure) recruitment of the hippocampus into the DMN is conflicting. Frings and colleagues (2009) reported reduced functional connectivity between posterior cingulate and left hippocampus in TLE patients with left mesial temporal sclerosis (MTS, n=8), but not for right hippocampus in TLE patients with right MTS (n=6). However, Zhang et al. (2010) found reduced recruitment of bilateral hippocampi into DMN for TLE patients with right MTS (n=27) but no difference in TLE patients with left MTS (n=25). Finally, Liao and colleagues (2010) reported reduced connectivity of DMN with bilateral hippocampi in TLE patients with bilateral MTS (n=20). These conflicting studies painted an incomplete picture of epilepsy’s influence on the DMN.

Methods
We sought to resolve these conflicting findings by modeling individual differences in DMN connectivity. Specifically, we sought to model the DMN’s recruitment of the ipsilateral hippocampus (the hippocampus of the epileptogenic hemisphere) relative to the contralateral hippocampus for each participant. We theorized that this approach of using each patient as their own control would
better control for clinical factors such as illness severity and duration, and medication regimen, all of which could impact group-level inferences. We recruited fifteen patients with refractory TLE (7 left-sided, 8 right-sided) and 23 healthy control participants. Independent component analysis mapped the default mode network in control participants, from which ten regions of interest were modeled including posterior cingulate cortex (PCC) and left and right hippocampi. We examined group differences in the bivariate correlation of PCC with each hippocampus after (a) coding each hippocampus as left or right, or (b) coding each hippocampus as ipsilateral or contralateral to the epileptogenic focus, as determined from EEG monitoring, PET, and structural MRI. [For the latter analysis, control participants were randomly coded as having a left (n=11) or right (n=12) focus.] Finally, each region's recruitment into the larger DMN was assessed with the graph theory metric of strength, the mean correlation of a region with all other network regions. Two-tailed t-tests assessed if each region's strength significantly differed between TLE patients and control participants (p<0.05 with false discovery rate correction for 10 regions).(Benjamini and Hochberg 2000)

**Diminished DMN Recruitment of Ipsilateral Hippocampus with TLE**

Patients with left TLE showed bilateral reductions in hippocampal correlations with PCC (p<0.015) relative to control participants, whereas patients with right TLE only showed reduced right hippocampal correlation (p<0.005). After recoding hippocampi by laterality, both hippocampi showed reduced functional connectivity with PCC in TLE patients relative to control participants; this reduction was most dramatic for the ipsilateral hippocampus (p<0.001) but also significant for the contralateral hippocampus (p<0.018). The increased significance may partially stem from combining left and right TLE groups into a single TLE group (n=15) after recoding hemispheres. Graph theory revealed reduced network strength for ipsilateral hippocampus (p<0.006) and ipsilateral parahippocampal gyrus (p<0.002) but not their contralateral homologues or any other brain region. The finding of reduced ipsilateral parahippocampal strength highlights the crucial advantage of data-driven approaches like independent component analysis and graph theory, as statistical approaches that require defining regions *a priori* (such as bivariate correlations) would have overlooked this key but unexpected finding.

**On the Horizon: Epilepsy Biomarkers and Predicting Treatment Response**

The asymmetrically reduced strength of ipsilateral hippocampus and parahippocampal gyrus in TLE patients may by a clinical biomarker for identifying epileptogenic foci from resting-state fMRI. Interestingly, fewer than half of our TLE patients evidenced hippocampal sclerosis, suggesting that reduced functional connectivity may precede discernible structural damage. Additionally, future work should relate pre-surgical functional connectivity to post-surgical cognitive outcomes, with the goal of identifying patients with refractory temporal lobe epilepsy who would most benefit from surgical interventions. Finally, independent component analysis and graph theory methods are readily adaptable to other functional neuroimaging techniques, such as EEG and MEG, whose finer temporal resolution offer stronger evidence for synchrony between neuronal clusters.

**Significance for Neuropsychologists**

Beyond the potential usefulness of rs-fMRI to aid in seizure localization and possible prediction of surgical outcome (including cognitive change), this technique can be wedded with traditional neuropsychological measures to study underlying neural networks of broad cognitive, sensory, and motor functions, and is already being used for surgical planning in some settings (e.g., mapping functional networks). It holds promise for distinguishing diagnostic groups (mild cognitive impairment versus Alzheimer’s disease), and prediction of recovery in a variety of patient groups. Although rs-fMRI is still in its relative infancy – and the neuroimaging community is still refining its application for clinical population – research into the default mode network may reveal more about the complex processes carried out by the brain than the “active” tasks that we routinely assess in clinical practice (motor, learning and memory, naming). Neuropsychologists may benefit from learning about these emerging techniques and concepts, becoming involved in their clinical and research applications whenever possible, and being available to contribute our knowledge of brain-behavior relationships to their implementation.

**Acknowledgments**

This research was supported by grants to Dr. Drane from the National Institute of Neurological Disorders and Stroke of the NIH (nos. K23 NS049100 and K02 NS070960). Additional salary support was provided to Dr. James by the National Center for Research Resources (award no. UL1RR029884) and the KL2 Scholars Program (award no. KL2RR029883).

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**References**


References (continued)

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Dr. Andrew James is an assistant professor at the University of Arkansas for Medical Sciences. His research seeks to map how the brain encodes normative variance in cognition and behavior in order to facilitate the translation of functional MRI into clinical decision making and patient care.

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Successful management of epilepsy is typically achieved through the use of antiepilepsy drugs (AEDs). Although the mechanism of AEDs varies across different compounds, they obtain their therapeutic effectiveness by diminishing cortical excitability. Unfortunately, a byproduct of diminished cortical excitability is a risk of cognitive impairment, which may present neuropsychologically as a mild encephalopathy associated with decreased processing speed/efficiency, decreased attention and impaired memory. Exceptions exist such as topiramate, which may affect language or executive function abilities. AEDs are also associated with risks of behavioral side effects such as irritability, hyperactivity, and depression. Although the medications are classified as antiepilepsy drugs since epilepsy is their primary therapeutic indication, some AEDs have approved indications for headache, neuropathic pain, and bipolar disorder. Further, many AEDs are used for off label indications for a variety of psychiatric diseases. Thus, it is important for neuropsychologists to anticipate AED use across a variety of clinical conditions in addition to patients with epilepsy.

It is convenient to conceptualize AEDs as a function of when they were approved, and AEDs generally fall into 3 categories. The oldest group of medications, those that were approved prior to the 1980s, include carbamazepine (Tegretol), ethosuximide (Zaronin), phenobarbital, phenytoin (Dilantin), and valproate (Depakote). The next generation of AEDs includes felbamate (Felbamate), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), pregabalin (Lyrica), tiagabine (Gabatril), topiramate (Topamax), trileptal (Oxcarbazepine), and vigabatrin (Sabril). The newest generation of AEDs include ezogabine (Potiga), lacosamide (Vimpat), perampanel (Fycompa), and rufinamide (Banzel).

In broad generalization, the greatest risk of cognitive side effects is associated with first generation drugs, and the greatest risk in this group is with phenobarbital, although phenobarbital is rarely used in developed countries of North America and Europe. With the exception of topiramate (and possibly zonisamide), the risks of second and third generation AEDs are thought to be less (e.g., lamotrigine compared to carbamazepine), or no worse than older generation medications (e.g., oxcarbazepine compared to carbamazepine), at least when examined on the group level (see Loring, Marino, & Meador, 2007, for a review). Because of individual differences in response to AEDs, all of the medications listed carry some risk of cognitive and behavioral side effects. Unfortunately, there are few randomized comparative studies, and relative risks of treatment have not been fully established. Further, due to individual patient differences, even in patients with good seizure control, cognitive side effects may be observed, and no medication should be considered to be free of risk. The area of pharmacogenomics will hopefully allow better individual risk characterization in the future.

Although the list of approved AEDs is long, the choice of specific AED is generally dictated by type of seizures and epilepsy syndrome, as well as the side effect profile. Thus, the likelihood of encountering a specific medication in regular clinical evaluations varies considerably. In pediatric cases in which generalized epilepsy syndromes are common, the AEDs most often encountered include ethosuximide, lamotrigine, and valproate. In adults and children with focal epilepsy, the most common AEDs include levetiracetam, lamotrigine, and oxcarbazepine, and for patients with difficult to manage epilepsy, topiramate is often considered a viable treatment option.

The behavioral side effect of irritability can often be identified based upon the interactions of parents or other family members. Although formal randomized trials are just now getting underway to examine behavioral side effects of AEDs in children with new onset focal epilepsy (http://clinicaltrials.gov/ct2/show/NCT01891890), multiple open label trials have identified the greatest risk of AED related irritability with levetiracetam. While some AEDs have been associated with depressive symptoms in more than 1% of treated patients (felbamate, levetiracetam, tiagabine topiramate, vigabatrin, and zonisamide), frequencies of less than 1% have been noted for others (oxcarbazepine, gabapentin, pregabalin, and lamotrigine), and newer AEDs with a high frequency of depressive symptoms in clinical trials may also increase the risk of self-harm or suicidal behavior in clinical practice (Andersohn, Schade, Willich, & Garbe, 2010). A FDA meta-analysis of randomized trials released in 2009 observed that AEDs as a class are associated with an increased the risk of suicidal thoughts and behavior resulting in the FDA issuing a class wide safety alert. Cognitive AED side effects are often difficult to establish since they occur against the backdrop of the cognitive comorbidity associated with the underlying biologic substrate underlying a person’s epilepsy. Multiple studies have confirmed the presence
of cognitive impairment at the time of epilepsy diagnosis, even in the so called “benign” epilepsy syndromes, and indicated that the cognitive difficulties are not simply the result of the cumulative effects of seizures or the disruptive effects of abnormal EEG discharges (Fastenau et al., 2009). The risks of side effects, both CNS effects including cognition and sedation, as well as systemic side effects (e.g., rash) tend to be greatest after initiating new treatment and then habituate over time. However, significant cognitive difficulty identified soon after treatment predicts later cognitive effects indicating that when significant cognitive difficulty is identified early in the treatment, longer term exposure is not necessary to determine whether meaningful cognitive side effects will continue even if they diminish over time (Loring, Williamson, Meador, Wiegand, & Hulihan, 2011).

A major criticism of neuropsychological outcomes of treatment intervention, which includes beneficial therapeutic effect for treatment of Alzheimer disease, is that the clinical meaningfulness of differences in neuropsychological test performances has not been clearly established for most measures. In fact, the absence of direct clinical correlation is the reason that the FDA requires a Clinical Global Impression of Change (CGIC) score rather than relying solely on neuropsychological score changes as endpoints to evaluate the efficacy of drugs to treat the cognitive impairment associated with Alzheimer disease. The Conners’ Continuous Performance Test (CPT), however, is a measure that is not only sensitive to the attentional effects of AEDs, but also includes the Confidence Index, an empirically derived measure that identifies the likelihood of a clinically relevant attentional impairment.

Using the Conners’ CPT Confidence to characterize attentional impairment in children with childhood absence epilepsy at the time of diagnosis, over one-third of children with CAE had impaired attention function that could not be attributed to medication effects, and thus reflected either primary or secondary disease effects (Masur et al., 2013). After being randomized to valproate, ethosuximide, or lamotrigine, nearly one half of the children taking valproate (49%) had impaired attention, significantly higher than either ethosuximide (32%) or lamotrigine (24%). Because individual CI performances allow the attention to be characterized as either impaired or not on the individual subject level, relative treatment risks can be calculated. Ethosuximide is associated with a 17% absolute risk reduction (95% Confidence Interval = 6%–28%) of impaired attention compared to valproate, the two comparably effective CAE treatments (Relative Risk Reduction = 35%, 95% CI = 13%–57%; Number Needed to Treat = 6, 95% CI = 4–16). Thus, for every 6 children with CAE treated with ethosuximide rather than valproate, impaired attention in one child is avoided. Because of valproate and ethosuximide were equally successful in treating CAE, but because ethosuximide was associated with less cognitive impairment, ethosuximide was the recommended initial treatment for CAE (Glauser et al., 2010).

Of the second and third generation AEDs, the greatest concern regarding cognitive side effects is associated with topiramate. In studies of patients with epilepsy and in healthy volunteers, the distinct cognitive side effects associated with TPM have been well-described and studied. In head to head comparisons, topiramate has been associated with higher risk of cognitive impairment than valproate, lamotrigine, levetiracetam, and is often associated with word finding and naming impairment (Gomer et al., 2007; Gross-Tsur & Shalev, 2004; Martin et al., 1999; Meador, Loring, Hulihan, Kamin, & Karim, 2003; Meador et al., 2005; Witt, Elger, & Helmstaedter, 2013).

Although the direct clinical relevance of Reliable Change Indices (RCIs) has not been established, RCIs establish whether individual performances exceed that which can be attributed to practice effects while accounting for test-retest retestabilities, and provide a valuable technique to characterize individual patient performances, and when used in dose-ranging studies, can be used to provide estimates of relative risks. Using this approach in a dose-ranging study of topiramate (Loring, et al., 2011), the risk of RCI cognitive decline for topiramate 64 mg and topiramate 96 mg dosing ranged from 8% to 12%. At topiramate 192 mg, approximately 15% of the subjects demonstrated significant RCI declines and at topiramate 384 mg, 35% of the subjects had declines. Thus, using the vocabulary of clinical drug trials in which RCI declines represent treatment-emergent cognitive side effects, this risk expressed as the number of patients treated in order to have one with significant cognitive decline, i.e., the number needed to harm (NNH) can be applied to the 4 doses studied: 64 mg NNH = 15.1, 96 mg NNH = 32.6, 192 mg NNH = 10.7, and 384 mg NNH = 3.3.

There has been little research with treatment randomization to study the effects of polytherapy on cognitive test scores; however, polytherapy is generally thought to reflect greater cognitive impairment compared to the cognitive side effects of monotherapy alone (Meador, 2005). Appropriate clinical trials have not been performed to precisely quantify risks and to examine the effects of different combinations of various compounds, and non-randomized trials are confounded by the fact that patients on polytherapy have more refractory epilepsy with greater underlying cognitive impairment associated with their epilepsy.

The clinical neuropsychological evaluation of epilepsy patients should include appropriate attention to the possible effects of AEDs, particularly with respect to processing speed such as that measured with Coding and Symbol Search with the Wechsler Intelligence Scales. Story memory measures such as Logical Memory tend to be more greatly affected by AEDs than list learning memory tasks due to the effects of attentional fluctuation and given the absence of multiple learning trials to compensate for attentional variability. As noted previously, the Continuous Performance Test is sensitive to attentional declines from AEDs. Although it is beyond the scope of this article to describe the language impairment attributed to topiramate, neuropsychological measures such as the Controlled Oral Word Association test (aka FAS) are often affected by topiramate. Recent medication changes associated with subject complaint of cognitive impairment combined with a neuropsychological pattern of performance inefficiencies on the measures described above are often sufficient to identify adverse treatment effects on cognitive function, and may alert the treating physician to the need to consider other treatment options.
**References**


Neuropsychologists at comprehensive epilepsy surgery centers provide a wide variety of services that usually include pre- and post-operative neuropsychological assessment, the intracarotid amobarbital (Wada) procedure, language assessment during functional magnetic resonance imaging (fMRI), and cognitive evaluations during electro-cortical stimulation mapping. Neuropsychologists have been designated as “essential personnel,” and neuropsychological assessment and Wada testing have been designated as “essential neuropsychological services,” for all epilepsy surgery centers by the National Association of Epilepsy Centers (2001). This article will focus on the role of the neuropsychologist in pre- and post-operative neuropsychological assessment and its importance for outcome in epilepsy surgery patients.

Patients are usually referred for preoperative neuropsychological assessment after video-EEG monitoring has been accomplished, and the seizure disorder has been adequately characterized with regard to etiology, seizure semiology, and EEG characteristics. The primary purposes of preoperative neuropsychological assessment within the epilepsy surgery context are to:

- help lateralize and localize the seizure focus,
- predict risk for postoperative cognitive impairment,
- establish a baseline against which to measure change, and
- help predict seizure relief outcome.

**Recommended Test Battery**

The National Institute of Neurological Disorders and Stroke (NINDS) formed an Oversight Committee in 2009 to update and direct further development of the Epilepsy Common Data Elements (CDEs). The neuropsychology subgroup was composed of eight expert epilepsy neuropsychologists who went through the literature and made recommendations regarding test administration to develop a more standardized approach to testing across epilepsy centers using validated instruments for specific domains. The NINDS epilepsy neuropsychology test recommendations for adults and children can be found by going to http://www.commondataelements.ninds.nih.gov/Epilepsy.aspx, and scrolling down to click on the hypertext “Download Epilepsy CDE Recommendations” to view all of the recommended domains (including neuropsychology). You will notice that there are separate listings for quality of life instruments and for tests measuring psychological-emotions factors.

**Purposes of Preoperative Neuropsychological Assessment**

**Lateralization and Localization**

The role of neuropsychology in the preoperative evaluation for possible epilepsy surgery can be particularly enjoyable for the clinician since it is one of the last bastions of neuropsychological practice where localizing information garnered from the assessment still matters. One of the major reasons to obtain preoperative neuropsychological testing is to assist in the lateralization and localization of the seizure focus (Kneebone, 2001). When a focal deficit pattern emerges on testing that is concordant with EEG identification of the epileptogenic zone, and with structural brain abnormalities on MRI, there is increased confidence in localization of the seizure focus as well as an increased likelihood of seizure relief after surgery.

Although the pattern of neuropsychological deficits is more sensitive to the brain damage that causes the epilepsy than it is to the presence of the seizure focus itself, the lesion and epileptogenic focus often (but not always) overlap. It is much more likely to obtain a focal deficit pattern on neuropsychological testing when there is an epileptogenic lesion than most idiopathic (presumed genetic) cases. In cases where no discernible brain abnormality is apparent, the neuropsychological effects of epilepsy are more subtle and may be more difficult to localize due to interference from the nonspecific effects of antiepileptic drugs, cognitive development factors, psychosocial issues, or subclinical epileptic spikes.

When data from neuropsychological testing is at odds with seizure localization using EEG, the reasons for this discrepancy should be thoroughly investigated since it could have implications for seizure relief and neuropsychological outcome. There are a variety of factors that can confound interpretation of test results. For example, brain lesions early in life may result in atypical functional organization of higher cortical functions, and this can result in “false localization” information on neuropsychological testing. Certain diffuse brain pathologies, such as traumatic brain injury or encephalitis, often present with diffuse patterns of cognitive impairment which may obscure focal patterns of cognitive impairment. In addition, the earlier seizures begin in life, the lower and more generalized the cognitive deficit performance patterns will be. This is thought to be due to early intractable seizures disrupting the normal acquisition of a wide range of cognitive functions regardless of the seizure onset location (Chelune, 1994). Similarly, specific developmental learning disabilities are common in childhood onset epileptic disorders, and these may conceal certain focal deficit patterns on testing.

**Risk for Postoperative Cognitive Impairment**

The risks that have been most thoroughly studied and that occupy the majority of the neuropsychologist’s time involve memory and language in temporal lobectomy candidates. After it was discovered that a unilateral temporal lobectomy could result in a dense global amnesia if the contralateral mesial temporal lobe is preserved, certain focal deficit patterns on neuropsychological testing when there is an epileptogenic lesion than most idiopathic (presumed genetic) cases. In cases where no discernible brain abnormality is apparent, the neuropsychological effects of epilepsy are more subtle and may be more difficult to localize due to interference from the nonspecific effects of antiepileptic drugs, cognitive development factors, psychosocial issues, or subclinical epileptic spikes.

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structures (especially the hippocampus) were dysfunctional, neuropsychological testing and Wada memory assessment have been used to determine the functional status of the hippocampus ipsilateral to the seizure focus (its so-called functional adequacy) as well as the functional capacity of the hippocampus contralateral to the seizure focus (the functional reserve) which will be responsible for the formation of new memories after temporal lobectomy (Loring & Chelune, 2001). Thus, the neuropsychological test patterns that suggest possible risk for global amnesia include impairments in both verbal and nonverbal memory, which imply bilateral hippocampal dysfunction, and material-specific memory impairments in the opposite direction to that expected on the basis of the seizure focus (e.g., verbal memory deficits in patients with right mesial temporal lobe seizures). In both these cases, the preoperative memory test results suggest the possibility of inadequate functional reserve on the side opposite to the proposed surgery. Wada memory asymmetries are considered better predictors of risk for amnesia than neuropsychological memory test results.

Prediction of Memory Loss
With regard to predicting material-specific memory losses after unilateral (especially left) temporal lobectomy, many studies have shown the higher the preoperative level of verbal memory capability, the greater the postoperative verbal memory loss. This has been well-established for verbal memory following left temporal lobectomy, but not for nonverbal, visual-spatial memory after right temporal lobectomy. The prediction of material-specific memory decline in the individual case is enhanced when the results of baseline neuropsychological memory tests are considered in conjunction with the results of other sources of information. Several mathematical risk models have been developed to predict postoperative memory decline. These risk models have incorporated variables found to be most critical in predicting postoperative memory outcome including side of surgery, presence of unilateral mesial temporal sclerosis on MRI, hippocampal volumetric analysis, age of epilepsy onset, memory ability during Wada testing, and level of preoperative memory performance. For example, Stroup, Langfit, Berg, et al. (2003) empirically developed a multiple regression equation for predicting memory decline which clinicians may use to estimate an individual patient’s risk for verbal memory decline following unilateral temporal lobectomy. Patients with the greatest risk had:

- dominant temporal lobectomy (left ATL),
- (2) absence of ipsilateral (to seizure focus) mesial temporal sclerosis,
- (3) normal preoperative performances on two tests of immediate verbal memory,
- (4) normal preoperative performances on two tests of delayed verbal memory, and
- (5) normal Wada memory after contralateral (to seizure focus) amobarbital injection.

Others consider the presence of mesial temporal lobe sclerosis on the side contralateral to the planned surgery to be an additional risk factor for cognitive decline after anterior temporal lobectomy.

Risk of Postoperative Language Impairment
Preoperative neuropsychological assessment of language typically evaluates fluency, naming, aural comprehension, and reading at a minimum. If there are specific concerns about language and other related domains a broader assessment may be conducted. For example, if language deficits are already present, then a more detailed assessment of language is warranted. This usually consists of selected subtests from one or more of the comprehensive aphasia batteries, such as the Boston Diagnostic Aphasia Examination (BDAE), Multilingual Aphasia Examination (MAE), or Western Aphasia Battery (WAB).

As with memory functions, higher preoperative language capacity has been associated with larger postoperative declines. Although acute aphasia is common in the acute postoperative period (usually lasting only a few days or weeks), significant language disorders are not often seen after dominant temporal lobectomy. Nonetheless, subtle deficits in naming are fairly common (estimates range between 25% and 40%). Language lateralization is determined using Wada testing or with ever increasing frequency fMRI. If the epileptogenic zone overlaps with areas of suspected language functions, patients may require more detailed electro-cortical stimulation mapping either intraoperatively or extraoperatively using subdural grids to identify eloquent language areas to be avoided during surgical resection.

Establish a Baseline
Although refractory patients who are candidates for epilepsy surgery almost universally have experienced significant disruption to daily life as a result of their seizure disorder, one of the purposes of a preoperative neuropsychological assessment is to help evaluate and quantify this impact. In addition to a broad based cognitive assessment, the preoperative evaluation also uses psychological-emotional tests, symptom checklists, self-report inventories, and health-related quality of life measures. These tests, in conjunction with the cognitive measures, attempt to characterize the impact of the seizures on patient’s lives to assist in determining if the epileptic disorder is of sufficient severity to warrant surgery.

Baseline assessment may also be used to track cognitive deterioration over time. Although somewhat controversial as to the cause of decline, there is strong evidence that repeated seizures have a deleterious effect on neural tissue. Seizure history variables that may influence cognitive decline include frequency of seizures, number of episodes of status epilepticus, early age of onset of seizures, total number of lifetime seizures, etiology, duration of seizure disorder, multiple seizure types, and use of antiepileptic medications (Chelune, 1994). If a patient’s condition is not severe enough to warrant epilepsy surgery, serial neuropsychological assessment may help to establish the eventual need for surgery. Finally, some epilepsy surgery patients experience cognitive deficits or develop new cognitive complaints after surgery and having documented a cognitive baseline allows us to estimate degree of change, if any, with greater precision. Postoperative neuropsychological evaluation will assist in identifying the cause(s) of the changes after surgery, which in turn, will determine the appropriate treatment recommendations.

Serial Neuropsychological Assessment
Change in test scores before and after epilepsy surgery may be influenced by a variety of factors in addition to the direct effects of brain tissue resection and reduction in seizure frequency. Other influences may include test-retest practice effects, changes in mood, improvements in quality of life, and measurement error. Methods that may be used to increase confidence of an individual’s postsurgical cognitive change include employing reliable change indices (RCIs), standard regression-based (SRB)
change score norms, equivalent alternate forms of a test, and using multiple tests to measure the same cognitive domain for convergent validation. RCIs and SRB norms have been developed for epilepsy surgery patients using many of the most commonly administered neuropsychological tests (Chelune, Naugle, Luders, et al., 1993; Hermann, Seidenberg, Schoenfeld, et al., 1996; Martin, Sawrie, Gilliam, et al., 2002).

**Prediction of Seizure Control**

In addition to seizure history variables (e.g., age of onset, duration of seizures, etiology), EEG characteristics, and MRI findings, neuropsychological test results also have been shown to hold prognostic significance for post-resection seizure control. Results over the past twenty years or so have consistently found that patients who have cognitive deficits restricted to the area of the proposed surgery are most likely to benefit from surgery (Rausch, 1987). There is also evidence that patients whose neuropsychological results suggest dysfunction is confined to a temporal lobe have better seizure relief outcome than those with test findings indicating extratemporal lobe dysfunction. Neuropsychological test results suggesting widespread cortical dysfunction in both hemispheres have been associated with poor postoperative seizure control. Consistent with this, studies across epilepsy surgery centers have found patients with low preoperative Full-Scale IQs have a worse prognosis for seizure relief than those with higher IQs. This is thought to be due to the fact that epilepsy surgery candidates with low IQs (FSIQ < 65) more often have early and more diffuse cerebral involvement. It is important to remember that neuropsychological test results do not have as much predictive power for seizure relief as some other test results, such as multifocal EEG abnormalities. For example, patients with low IQs are not routinely excluded from surgery at most institutions, but this neuropsychological predictive information is often considered as one part of the entire puzzle of presurgical test results and could assist with surgical decision-making.

Similar to neuropsychology practice in other specialty areas, the neuropsychologist’s task in epilepsy is to interpret the pattern of deficits across tests to understand the relative contributions of each of the seizure history variables to assist with prediction of surgical outcome and other aspects of treatment planning. The neuropsychologist attempts to integrate test data, history, clinical interview, behavioral observations and available laboratory and neuroradiological evidence into one cohesive summary report that arrives at a neurobehavioral diagnosis, discusses the neurological and psychological implications, and informs other medical professionals about follow-up treatment and management.

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**References**


Whether you are a pediatric neuropsychologist or an adult neuropsychologist, childhood-onset epilepsy is likely to show up in your clinical practice and training activities. Epilepsy is one of the most common neurological disorders, and a large proportion of people with epilepsy have their onset during childhood or adolescence with long-term consequences that can extend into adulthood. Epilepsy is more than seizures: Epilepsy often affects cognitive, academic, emotional/behavioral, and social functioning; it affects sleep, which can have indirect effects on these areas of functioning; it can require treatments that sometimes can produce adverse cognitive and behavioral changes; and the family is affected by the seizure condition, and the family can contribute – positively and negatively – to outcomes in children with epilepsy. This brief article presents an overview of epilepsy and its comorbidities and the roles of neuropsychologists; these topics are discussed in much more detail elsewhere (e.g., Fastenau, 2010, 2014; Fastenau, Dunn & Austin, 2004).

Overview of Epilepsy
Epilepsy is a condition characterized by multiple unprovoked seizures, that is, seizures that are not due to transient precipitants such as fever or electrolyte imbalance. Approximately 1% of the population develops epilepsy by age 20. Of these, 10% develop epilepsy before age 1; very early onset is often associated with severe generalized, symptomatic syndromes accompanied by developmental delays, cerebral palsy, or other neurological deficits. The vast majority of children develop epilepsy after age 1, with a higher proportion of partial seizures (seizures with focal onset) and fewer catastrophic syndromes (Hauser, 2001). Approximately 1/3 of children with epilepsy have symptomatic etiology (i.e., associated with structural abnormality); 2/3 have idiopathic/genetic or cryptogenic/unknown etiology (Theodore et al., 2006). Febrile seizures (occurring in 4% of children) warrant special attention in the history by a neuropsychologist who is entertaining the possibility of undiagnosed epilepsy; they are benign if they do not develop into epilepsy (Chang, Guo, Huang, Wang, & Tsai, 2000); however, the risk for developing epilepsy increases from 2% (with simple febrile seizures) up to 13% when other risk factors are present: febrile seizures lasting >15 min or that have focal signs or that recur within 24 hrs; family history of afebrile seizures; neurodevelopmental abnormalities prior to 1st febrile seizure; abnormal EEG at time of febrile seizure; febrile seizure after age 3 (and risk doubles for febrile seizures occurring after age 5 (Berg et al., 1992; Grattan-Smith, Harvey, Desmond, & Chow, 1993; Provenzale et al., 2008; Scott et al., 2002; Tsai & Hung, 1995; Verrotti et al., 2000; Vestergaard et al., 2007; Voudris et al., 2002).

Neuropsychological Functioning
Neuropsychological profiles can vary widely in epilepsy. People with severe generalized syndromes (typically with very early age of onset) often have broad intellectual deficits and developmental delays. However, the majority of people with childhood-onset epilepsy have intellectual functioning in the normal range with more specific neuropsychological deficits. Some deficits are more ubiquitous in this population (attention, psychomotor speed, memory); however, a wide range of deficits can be associated with focal epilepsy corresponding with the substrate of the seizure focus.

These deficiencies can appear at or soon after onset. Several studies have documented neuropsychological deficits at or near onset in children with epilepsy (Fastenau et al., 2009; Hermann et al., 2006; Oostrom et al., 2003; Stores et al., 1992). Our team followed 350 children from their first identified seizure and 253 healthy sibling controls for 3 years (Fastenau et al., 2009). At onset, 27% of the children with seizures scored at least 1.3 standard deviations below the siblings on one or more neuropsychological domains; this rose to 40% for children with risk factors, including multiple unprovoked seizures (i.e., epilepsy diagnosis), symptomatic etiology, use of antiepileptic medications, and epileptiform activity on the initial EEG; sleep problems and childhood absence epilepsy also increased the risk of having neuropsychological deficiencies (Byars et al., 2007; Byars et al., 2008; Fastenau et al., 2009).

Adverse neuropsychological changes can occur over time for a subset of this population. When we followed our cohort over time, processing speed slowed down (or did not keep pace with siblings), especially for those with seizures that predated diagnosis, undercontrolled seizures (as few as 1 seizure per 9 months), and use of antiepileptic medication throughout the 3-year follow-up period (Fastenau et al., under review). Three other neuropsychological studies followed children longitudinally from onset of epilepsy. Bourgeois and colleagues (1983) observed a decline in IQ over 4 years for normally developing children; at risk were children with uncontrolled seizures, toxic levels of antiepileptic drugs (AEDs), and younger onset. Oostrom and her colleagues (2005) noted delays or declines in spatial learning, working memory, and attention. Hermann and colleagues (2008) observed lack of improvement on executive tasks over the first 2 years, but only in those with comorbid ADHD or academic problems at onset. Other studies followed children longitudinally starting later in the disorder; IQ declines (especially Performance IQ) were associated with undercontrolled seizures and phenobarbital levels (Bjornaes et al., 2001; Rodin et al., 1986).
**Comorbidities of Childhood-Onset Epilepsy**

Childhood onset of epilepsy is associated with several comorbidities. Mental health problems have been reported in 26%–29% with uncomplicated epilepsy, approximately five times higher than the general population and 2.5 times higher than other chronic illnesses; rates are doubled when other neurological abnormalities are present (56%–58%). Especially common are anxiety (30%–40%), depression (~25%), and attention-deficit/hyperactivity disorder (ADHD, 25%–40% of children with epilepsy), predominantly inattentive subtype (Davies, Heyman, & Goodman, 2003; Dunn, Austin, Harezlak, & Ambrosius, 2003; Rutter, Graham, & Yule, 1970); behavior problems can be evident at diagnosis, especially for children who have been having seizures prior to diagnosis (Austin et al., 2001). Because behavior problems tend to be internalizing and the ADHD symptoms are mostly inattentive (thus, not behaviors that draw attention by others), these problems are often unidentified and untreated in these individuals (e.g., Fairbanks, Cunningham, Fastenau, Austin, & Dunn, 2006).

Academic problems are also common. As a group, children with epilepsy earn lower grades, score lower on achievement tests, repeat grades, are placed in special education, and are diagnosed with learning disability (LD) more often than other children (Farwell, Dodrill, & Batzel, 1985; Dunn, Johnson, & Atkinson, 1995; Mitchell, Chavez, Lee, & Guzman, 1991; Seidenberg, et al., 1986). We conducted a large community-based study of children who had had epilepsy for an average of 5 years; 48% met psychometric criteria for learning disability (Fastenau, Shen, et al., 2008). In a population-based study in the UK, rate of epilepsy was 30 times higher among children in special education compared to children in mainstream settings (Tidman, Saravanan, & Gibbs, 2003).

Social problems can also be apparent, especially as children with epilepsy transition through adolescence and into adulthood. As adults, they have a higher risk of being unemployed or underemployed, unmarried, and living with parents (Kokkonen, Kokkonen, Saukkonen, & Pennanen, 1997; Sillanpaa, Jalava, Kaleva, & Shinnar, 1998; Wakamoto, Nagao, Hayashi, & Morimoto, 2000), especially if their seizures are not optimally controlled (Sillanpaa, Haataja, & Shinnar, 2004).

Of particular importance to the neuropsychologist, cognitive deficiencies are associated with — and might contribute to — most of these comorbidities. In our prospective longitudinal study, as neuropsychological functioning declined over time, there were concomitant delays/declines in academic functioning (Dunn et al., 2010), increases in depression and behavior problems (Austin et al., 2010, 2011), and declines in social skills (Byars et al., 2014). Furthermore, family factors influence the impact of neuropsychological deficits on these outcomes, both positively and negatively (e.g., Dunn et al., 2010; Austin et al., 2011; Fastenau et al., 2004).

These background data about epilepsy have major implications for neuropsychologists. We play a major role in diagnosis of epilepsy, identification of comorbidities, and intervention.

**Assessment**

Seizures go unrecognized for months or even years prior to diagnosis for approximately 1/3 of children (Austin et al., 2001; Fastenau et al., 2009; Shinnar et al., 1990). Since many of these children are referred to neuropsychologists for evaluation of ADHD and LD, we might be the first professionals to identify symptoms as seizures. Therefore, neuropsychologists need to be alert to the possibility of epilepsy when evaluating children referred for learning challenges and need to inquire into risk factors and possible symptoms. Even among children with diagnosed epilepsy, neuropsychologists need to assess for neuropsychological deficiencies and for the academic, social, and mental health comorbidities described above. Finally, when a neuropsychologist sees a pattern of cognitive regression in a child with a history of seizures or risk for epilepsy, this could reflect underlying epileptiform discharges and can prompt further electrophysiological studies (see Fastenau, 2011b for further description of this phenomena, clinical syndromes, and implications for treatment).

**Intervention**

Epilepsy intervention is first directed toward controlling seizures. The majority of people with epilepsy will be treated with antiepileptic medications. Among the older medications, phenobarbital has been associated with cognitive side effects, as well as phenytoin and barbiturates to a lesser degree. Among the newer medications, topiramate has been associated with cognitive difficulties, whereas the others appear to have limited adverse cognitive effects. However, these statements are based largely on studies of monotherapy and group-level analyses; any individual child might experience adverse cognitive effects on any medication or due to interactions among medications. Therefore, cognitive complaints must be monitored and clinically correlated with medication changes for each child individually (Bourgeois, 2004; Ortinski & Meador, 2004).

Among children and adults who have onset of epilepsy in childhood, 23% develop seizures that cannot be controlled pharmacologically, even on multiple antiepileptic medications (Berg et al., 2006). More aggressive therapies are considered in these circumstances, including resective surgery (focal cortical resection, callosotomy, hemispherectomy), multiple subpial transection, and electrical stimulation (vagal nerve stimulation, deep brain stimulation, and responsive neurostimulation system); descriptions of these procedures and a detailed analysis of neuropsychological outcomes following surgery are available elsewhere (e.g., Busch, 2011; Fastenau, 2011a; Helmstaedter, 2011; Sherman et al., 2011). Neuropsychologists at epilepsy centers providing these therapies perform many special roles, such as assessing candidacy for the procedure, predicting outcomes, evaluating language lateralization (e.g., Wada exam, fMRI), assisting with electrocorticography, and assessing postsurgical changes/needs and planning rehabilitation.

The ketogenic diet is another intervention for medically-refractory seizures. Although “diet” sounds benign, this therapy carries significant health risks and should be conducted only under the direction of a medical team specialized in this therapy (Kossoff, Rho, Kossoff, & Rho, 2009; Kossoff, Zupec-Kania, Amark, et al., 2009; Kossoff, Zupec-Kania, Rho, et al., 2009). Neuropsychologists can also intervene to help people with epilepsy understand the impact of nonmedical factors on seizure control and to help change behaviors to improve seizure control and outcomes. Stress (Reddy, Rogawski, Reddy, & Rogawski, 2002), poor sleep habits or sleep disorders (Malow, 2005), medication nonadherence (Mitchell, Scheier, & Baker, 2000; Sheth & Gidal, 2006), and heavy caffeine and alcohol consumption...
Depression Symptoms in Children with Seizures: Relationships with
Austin, J. K., Perkins, S. M., Johnson, C. S., Fastenau, P. S., Byars,
prospective investigation.
al. (2006). How long does it take for epilepsy to become intractable? A
Berg, A. T., Shinnar, S., Hauser, W. A., Alemany, M., Shapiro, E. D., Salomon,
England Journal of Medicine, 327(16), 1122–1127.
al. (2006). How long does it take for epilepsy to become intractable? A
prospective investigation. Annals of Neurology, 60(1), 73–79.
Bjornaes, H., Stabell, K., Henriksen, O., & Loyning, Y. (2001). The effects
of refractory epilepsy on intellectual functioning in children and adults. A
longitudinal study. Seizure, 10, 250–259.
Bourgeois, B. F. (2004). Determining the effects of antiepileptic drugs on
cognitive function in pediatric patients with epilepsy. Journal of Child
Neurology, 19(Suppl. 1), S15–S24.
References
Austin, J. K., Harezlak, J., Dunn, D. W., Huster, G. A., Rose, D. F., & Ambrosius,
Austin, J. K., Perkins, S. M., Johnson, C. S., Fastenau, P. S., Byars,
Austin, J. K., Perkins, S. M., Johnson, C. S., Fastenau, P. S., Byars, A. W.,
Bourgeois, B. F., Prensky, A. L., Palkes, H. S., Talent, B. K., & Busch, S. G.
Byars, A. W., deGrauw, T. J., Johnson, C. S., Fastenau, P. S., Dunn, D. W.,
Byars, A. W., deGrauw, T. J., Johnson, C. S., Fastenau, P. S., Perkins, S.
Chapieski, L, Brewer V, Evankovich K, Cilanh-Shelburne K, Zelman K,

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(Bonilha & Li, 2004; Kaufman & Sachdeo, 2003; Gordon & Devinsky, 2001) can lead to breakthrough seizures. In women, the menstrual cycle can affect the seizure threshold (Spector, Cull, & Goldstein, 2000); thus, managing these other factors can be especially critical during that time period. In addition to seizure control, nonadherence has been associated with a variety of adverse clinical and social outcomes (Hovinga et al., 2008). The children’s reactions to their new medical condition and various family factors (maladaptive parent reactions; home environments that are disorganized, unstructured, and emotionally unsupportive) can have negative and positive effects on outcomes (e.g., Austin et al., 2010; Austin et al., 2011; Chapieski et al., 2005; Dunn et al., 2010; Fastenau et al., 2004); consequently, seizure education and family therapy can help to improve a variety of outcomes.

Conclusion
Childhood-onset of epilepsy is a relatively common condition in pediatric and adult neuropsychology settings. Neuropsychologists play critical roles in helping to diagnose epilepsy, assessing risks and manifestations, and intervening to improve seizure control and psychosocial outcomes.
Detection with MR imaging.


References (continued)


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Aging in Epilepsy: Cognition and Brain Structure

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The Challenge
Epilepsy is the fourth most common neurological disorder, representing a diversity of syndromes of variable seizure frequency and severity and impact on cognition, behavior, and quality of life (Institute of Medicine, 2012). Many individuals with childhood epilepsy are well controlled with anti-epilepsy medication (AED), and characterized by minimal impact on cognitive and brain development. However, there is a distinct subset of individuals who remain refractory to treatment and experience a chronic and long-standing course of seizures. Given the known age-related cognitive changes as well as the structural and functional brain changes that occur, it is possible that these people are more vulnerable as they get older.

In this brief paper, we provide an overview of current findings on this topic primarily focusing on work from our lab. There are three subgroups of older people of relevance for investigation. These include individuals with an onset of epilepsy at an early age (e.g., < 20 years). This is the group which is the focus of this paper. Other important subgroups include individuals who begin to have new onset recurrent seizures as adults (e.g., over age 50). Finally, there is a group of individuals with epilepsy secondary to another acute neurological event (e.g., stroke, traumatic brain injury). Recent papers on these latter topics are available (Roberson et al., 2011; Lowenstein, 2009).

Paucity of Research
We currently know very little about the course of cognition and brain structure in aging people with childhood/adolescent onset epilepsy. This is notable as the incidence and prevalence of epilepsy in people over aged sixty has markedly increased and estimates indicate further increases can be expected. The mean incidence and prevalence rates of epilepsy in older people are 2.4 per 1000 and 10.8 per thousand, respectively. There is a lifetime risk of epilepsy of 1.6% up to age 50 years and 3.4% to age 80. In addition, there is increasing evidence of a relationship between Alzheimer’s Dementia (AD) and epilepsy including high rates of co-morbidity and the possible similarity of cellular mechanisms underlying both disorders.

The dearth of clinical neuropsychological research of aging and epilepsy is very evident. We offer two possible reasons for the imbalance of neuropsychological investigation directed to the younger age population compared to the elderly, both of which pertain to issues relevant to the clinical neuropsychology of epilepsy. First, the onset of epilepsy often occurs before the age of eighteen years. This is primary time point for a comprehensive diagnostic work-up including assessment of cognitive functioning to be facilitated by a network of advocacy provided by parents, health care professionals, and social agencies invested in ensuring that these children obtain the most optimal intervention services. This is particularly the case for school aged children. Unfortunately, the cost and lack of resources often make it difficult to obtain follow-up assessment unless significant academic or psychiatric difficulties are identified.

Perhaps the most studied issues in the neuropsychology of epilepsy revolve around the population of TLE individuals being seen for possible surgery to relieve chronic and intractable seizures. Surgical intervention, particularly anterior temporal lobectomy (ATL) has proven to be a viable and effective intervention approach for these individuals. Neuropsychology has played a significant role in the clinical assessment of these patients both before and after surgery. Research with this population has provided important information about the neurobiological basis of cognition, particularly on the role of the hippocampus and surrounding MTL on declarative memory, language dominance, plasticity and reorganization, and material-specific memory. However, ATL is typically conducted for individuals between 20-50 years of age (mean age in the mid 30’s). Thus, this population is not appropriate to study the natural course of epilepsy and aging.

Growing Old with Epilepsy
Several years ago, we published a paper which highlighted the relative lack of research regarding cognitive and brain structure aging in older adults with chronic epilepsy (Hermann et al., 2007). Discussed were a number of risk factors (e.g., vascular and lifestyle factors), shown to be associated with cognitive decline in aging people in the general population, risk factors that also appear to be elevated in persons with chronic epilepsy. In the general population, there is considerable evidence that vascular risk factors and vascular disease including higher rates of hypertension, ischemic heart disease, heart failure, diabetes, and cerebrovascular disease have a deleterious impact on cognitive aging. This is a concern as population-based surveys document higher rates of these medical problems in persons with epilepsy. In addition, there is considerable evidence that lifestyle habits that may protect against these risks such as physical exercise, weight control, cognitive stimulation, and social integration are less likely to characterize the lives of people.

Despite these concerns, there are only a handful of published studies that have directly examined the neuropsychological functioning of epilepsy in individuals over the age of sixty.
These studies consistently point to poorer cognitive functioning compared to a control group. Of interest, Griffith et al., (2005) compared the cognitive performance of older individuals with epilepsy (over age 60) to a comparable age MCI group, a group known to be at increased risk for conversion to AD. The epilepsy group showed a similar degree of impairment across the subscales including the Memory scale compared to the MCI group.

**Current Hypotheses**

Historically, the study of age-related changes in cognition and brain structure was conceptualized in terms of progressive decline (neurodegenerative effect). From a neuropsychological perspective, the progression hypothesis entails the possibility that cognitive decline becomes increasingly evident with increased duration of the disorder. Early neuropsychological studies supported the progression hypothesis with cognitive decline exhibited by a subset of investigated cohorts. Cognitive impairment among adults with chronic epilepsy was reported in the context of a high cumulative frequency of seizures (particularly tonic-clonic), severity of seizures, number of status episodes, early age of onset, and longer duration of epilepsy. However, more comprehensive reviews indicated that the findings were mixed and in many instances it proved difficult to isolate duration of epilepsy from other factors (Dodrill, 2004; Seidenberg et al., 2007).

In contrast to the progression hypothesis, several recent papers have proposed a life-span perspective of chronic epilepsy, aging, cognition, and brain structure (Hermann et al., 2007; Helmstaedtor et al., 2009; Seidenberg & Hermann, 2010). From this perspective, chronic childhood onset epilepsy potentially impacts both early cognitive and brain development; an impact that is evident at time of initial diagnosis. In addition, these early outcomes in of themselves may have negative lifespan implications for academic and social-emotional development including aging effects on behavior.

At this point, the data available on this issue is primarily cross-sectional, with a focus on memory, and the study of individuals many years (even decades) after the onset of their epilepsy that is often intractable to conventional AED treatment. Fortunately, there has been a few published longitudinal investigations over the past few years. Furthermore, there has been a marked increased in neuroimaging studies.

**Cross-sectional Studies**

For many years, the study of cognitive dysfunction in chronic epilepsy primarily focused on the memory impairment observed in people with temporal lobe epilepsy (TLE). More recently, however, it has become evident that a picture of more generalized cognitive dysfunction is present, even among those with focal mesial temporal lobe seizures. We compared the performance of adults with TLE divided into a group with histopathological evidence of hippocampal sclerosis to TLE participants without such evidence (Hermann et al., 1997). Findings showed considerable generalized cognitive impairment in the former group including in domains of intellectual functioning, language, and visuoperceptual functions. In addition, the group with hippocampal pathology was characterized by an earlier age of epilepsy onset and longer epilepsy duration. Oyegbile et al (2004) examined duration of epilepsy and cognition in a sample of 96 subjects with chronic temporal lobe. Neuropsychological performance was adjusted for age, gender, and education based on the scores obtained from a group of 86 healthy controls. As expected duration effects were evident; more years of epilepsy was negatively correlated with performance in memory, language, visuoperceptual, and motor tasks. Of interest, duration effects were moderated by education level. Less educated individuals showed a stronger negative relationship between cognition and duration than a more educated group. One is left to consider the possible reasons for finding generalized cognitive impairment in a focal neurological group (TLE). In addition, it is possible that the moderating effect of education level may signal the impact of epilepsy on a developing brain, and/or the accumulative effects of years of intractable epilepsy.

More recent studies have provided support for the life span neurodevelopmental hypothesis. Christoph Helmstaedtor and colleagues (2009) reported a comparison of age regression performance in 1156 TLE patients and 1000 controls on a measure of verbal memory and learning. Notably, the age range for the two groups went from age 6 years old to age 70 years. They did not find a linear increase of divergence in performance across the age range as would be expected based on the progression hypothesis. Rather, there were significant differences between groups evident in the youngest age group which were accentuated until ages in the 20-30 year old range, and thereafter showed a parallel trajectory (thru age 70). Baxendale et al., (2010) reported similar findings in a retrospective study of three different aged cohorts. They also suggested that duration effects may be minimal and that the early age of epilepsy onset is more important. However, both of these studies use retrospective cross-sectional designs.

**Longitudinal Findings**

We followed a cohort a cohort of chronic TLE individuals, with a mean age in the late 30’s, a protracted duration of over 20 years, and a mean age of epilepsy onset of twelve years of age. They were compared to a healthy control group at two time points separated by four years. Measures of cognition and MRI scans were collected at both time points. At baseline, the chronic TLE group demonstrated significant impairment in a broad set of cognitive domains that extended beyond episodic declarative memory, and included difficulties with executive functioning, semantic memory and knowledge, language, and psychomotor ability (Hermann et al., 2002). As expected, baseline brain volumes were smaller in the TLE group in the hippocampus and other regions of the mesial temporal lobe. However, areas distal to the seizure focus (ipsilateral and contralateral) also showed smaller volumes than controls (Pulsipher et al., 2007). This may help explain the pattern of generalized cognitive impairment discussed earlier.

After four years, there was no evidence of significant cognitive decline in the TLE group. Overall their mean performance was quite stable across the four year interval. However, the healthy control showed a small improvement, presumably representing a practice effect on many of the cognitive measures. When the TLE group was examined more closely, it became apparent that a distinct subset of the participants did show an adverse and significant decline in test performance, as reflected by at least a two standard deviation (lower) than expected based on regression based change scores. The percent of participants affected ranged from under 25% in most domains, but the number of participants was higher on measures of confrontation naming (38%), immediate and delayed auditory-verbal memory (38%), and speeded motor dexterity (63%). Predictors of adverse cognitive outcome also varied across cognitive domains. For example, hippocampus volume was related to memory outcome, and total white matter volume for psychomotor speed (Hermann et al., 2006). In addition, demographic variables (chronological age,
education), seizure related variables (age of onset, duration, and number of AEDs) were significant predictors in several domains. It is important to note that the TLE sample was still quite young and many years away from the expected impact of age on cognition.

Given the heterogeneity of cognitive profiles shown by these participants, we used cluster analysis to determine if distinct cognitive phenotypes could be found. Three distinct cognitive profiles were identified in the TLE group: Cluster 1 consisted of 47% of the TLE subjects who showed minimal cognitive difference to the healthy controls, Cluster 2 consisted of 27% of the sample and was characterized by predominantly memory performance, and Cluster 3 subjects consisting of 29% of the TLE subjects showed poor performance across all cognitive domains. When these three cluster groups were examined at the four year evaluation, different patterns of prospective change were evident. Cluster 3 subjects who were the most impaired at baseline also showed the greatest four-year cognitive decline whereas the best cognitive course was seen for Cluster 1 subjects. Cluster 3 subjects also showed greater volume abnormality at baseline than the other two groups. Overall, the best volumetric predictor of cognitive change over the four year interval was increased ventricular enlargement (Hermann et al., 2007).

**Summary**

We have provided a very brief overview of current neuropsychological findings on aging and cognition and brain structure in chronic intractable epilepsy. Although many pieces still remain to be clarified, there is growing support for a lifespan perspective. In this context, childhood onset epilepsy is associated with abnormalities in cognition and brain structure that are apparent in early adulthood. Recent findings from our group indicate that the neurobiological substrate is compromised at the time of epilepsy diagnosis and quite possibly earlier (Hermann et al., 2008). It is quite possible that these abnormalities are compounded if education and social opportunities are negatively impacted in subsequent years. For these people, the normal age-related changes expected in cognition and brain structure may serve as an additional “insult”. An important objective of the lifespan perspective is to achieve a better understanding of what happens as these people get older. Neuropsychologists are well suited to this goal.

**References**


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Robert A. Stern, Ph.D.
BU Alzheimer’s Disease Center; Boston University School of Medicine
Chronic Traumatic Encephalopathy (CTE) in 2014: What We Think We Know and What We Need To Know

Closing Keynote Address:
Daniel L. Schacter, Ph.D.
Harvard University
Constructive Memory and Imagining the Future

Additional Highlights Include:
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• Military Concussion
• Creativity/Giftedness
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