Evidence-based Neuropsychological Assessment for Patient’s with Pharmacoresistent Epilepsy

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Objectives

- Neuropsychological Assessment in Epilepsy
  - Predicting outcomes
  - Assessing neurobehavioral comorbidity of epilepsies
- Neuropsychological Tests per domain
  - Common Data Elements
    - General Cognitive/IQ
    - Attention/executive
    - Language
    - Memory
    - Memory
    - Visuoperceptual/constructional
    - Motor
    - Mood
- Evidence-based Medicine For Neuropsychology in Epilepsy
  - Predict memory/language outcome
  - Predict Seizure outcome
What is Neuropsychology

- Neuropsychology is a discipline and a science.
- Study of brain-behavior relationships
  - Identify neuropsychological correlates of brain function
- Neuropsychology practice combines behavioral neurology with the psychometric foundations of psychological science and measurement.
Historical Overview of Neuropsychology

• Origins of Neuropsychology
  – Relationship to Behavioral Neurology
    • Functional Anatomical Correlation
    • Cortical Localization/Lateralization
  – Relationship to Psychology
    • Normative comparisons
    • Quantifying Brain Functions
    • Standardized tests
Historical Overview of Neuropsychology

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  - Standardized tests
Patient H.M.

• Henry Molaison (2/26/26-12/2/08)
  – High school graduate. Worked as a motor winder
  – Medication refractory epilepsy since age 10 YO
    • Nonlocalized partial and generalized seizures
    • Disabled by seizures and, likely, high doses of medications.

• Bilateral temporal lobectomy by William Scoville (1953) at 27 YO
Patient H.M.

- Sig. sz reduction but had dense antegrade amnesia
  - Studied since mid 50’s by Dr. Brenda Milner and others
- Advanced understanding of learning/memory and their neuroanatomical correlates
Neuropsychology in epilepsy

- Neuropsychology in Epilepsy Centers has long tradition
  - Improve **cognitive**, emotional, and functional outcome from treatment of epilepsy.
    - **Predict cognitive outcome from surgery**
    - Avoid profound amnestic syndrome (patient HM and others)
    - Study of functional neuroanatomical organization of memory
    - **Document cognitive effects of treatment (AEDs/VNS)**
  - Assist in localization/lateralization of brain dysfunction
  - Predict seizure freedom in some limited cases (MRI negative)
  - Identify treatment needs (speech/cognitive rehab, meds, OT/PT, work/school accommodations, etc.)
  - Answer questions about capacity
    - **Return to Work, ability to live independently, Driving, Etc.**
Why do doctors and patients care about cognitive aspects of epilepsy?

Clinical Perspective -
• Treatment goal to eliminate seizures, and improve:
  – (prevent decline in) cognitive function,
  – (not adversely affecting) behavior/mood,
  – Quality of life.
• Cognitive and psychiatric comorbidity:
  – Reduces treatment effectiveness
    • Cognitive complaints associated with d/c’d AED in up to 40% of patients
  – Increases costs of care
  – Decreases Quality of life

Research/Theoretical Perspective -
• Better characterize/predict manifestations of neuropathology
Non-independent factors affecting cognitive function in epilepsy

Aldenkamp AP. Seizure 2006
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- Cognitive/behavioral effects of AEDs
NINDS Common Data Elements

- Established set of disease and outcome variables for specific diseases – INCLUDING EPILEPSY
- To much variability in research assessing epilepsy
- Provide guidance for neuropsychological measures to include in research
- Neuropsychological tests with evidence-base in epilepsy for Adults and Pediatric Patients
- Include tests in:
  - General Cognitive/IQ
  - Attention/executive
  - Language
  - Memory
  - Visuoperceptual/constructional
  - Motor
  - Mood
  - Quality of Life
General Cognitive (IQ) function

- Why given?
  - Adults
    - Indicator of General capacity
  - Pediatrics
    - Strongly lateralized findings in children, predictive of seizure freedom
    - Required for School accommodations and determination of learning disability

- Adults
  - Wechsler Abbreviated Scale of Intelligence (WASI)
  - Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV)

- Pediatrics
  - WASI or 2nd Ed. (WASI-II)
  - Wechsler Intelligence Scale for Children-4th Ed. (WISC-IV)
  - Wechsler Preschool and Primary Scale of Intelligence-4th Ed. (WPPSI-IV)
  - Differential Ability Scales-2nd Ed. (DAS-II)

- Infants/toddlers
  - Bayley Scales of Infant and Toddler Development-3rd Ed. (Bayley-III)
Speed: Processing and Psychomotor Speed

• Why given?
  – Adults
    • Indicator of General cognitive function
    • Diagnosis and Treatment planning
  – Pediatrics
    • Predictive of long-term outcome and academic achievement
    • Diagnosis and Treatment planning

• Adults
  – WAIS-IV Digit Symbol and Symbol Search subtests
    • Processing Speed Index
  – CPT-II Hit Rate Reaction time
  – Grooved Pegboard Test
  – Finger Tapping Test

• Pediatrics
  – WISC-IV Digit Symbol and Coding subtests
    • Processing Speed Index
  – CPT-II Hit Rate Reaction Time
  – Grooved Pegboard Test
  – Finger Tapping Test
  – WRAVMA Pegboard Test
Attention & Executive Tests

- **Attention**: focused, selective, divided, sustained
- **Executive**: reasoning, problem solving, inhibition, planning, initiation, and maintenance of behavior
- **Why given?**
  - **Adults**
    - Indicator of capacity/competency and maybe used for lateralization/localization
  - **Pediatrics**
    - Indicator of localization/lateralization
    - Used in diagnosis of Attention Deficit Hyperactivity Disorders (ADHD)
    - Predictive of school adaptation and adaptive skills
Attention/Working Memory

**Adults**

**Focused/Selective Attention:**
- Wechsler Digit Span subtest
- Trail Making Test, Parts A & B
- Delis-Kaplan Executive Function System (DKEFS: Trail Making)
- Stroop Word & Color
- Test of Everyday Attention (TEA)

**Divided Attn/Working Memory:**
- Wechsler Digit span backwards
- Wechsler Letter/# sequencing

**Sustained Attention/Vigilance:**
- Conners’ Continuous Performance Test-2nd Ed. (CPT-II)

**Pediatrics**

**Focused/Selective Attention:**
- Wechsler Digit Span Subtest
- Trail Making Test, Parts A & B
- DKEFS: Trail Making
- Stroop Word and Color
- Test of Everyday Attention for Children (TEA-Ch)

**Divided Attn/Working Memory:**
- Wechsler Digit span backwards
- Wechsler Letter/# Sequencing

**Sustained Attention/Vigilance:**
- CPT-II
- Conners’ Kiddie Continuous Performance Test (K-CPT)
- Test of Variable Attention (TOVA)
Attention: Trails A
Executive Function Assessment

• **Adults**
  - Sequencing/Set-shifting
    - Trail Making Test, Part B
    - Wisconsin Card Sorting Test-64 Ed. (WCST-64)
    - Delis-Kaplan Executive Function System (DKEFS: Trail Making)
  - Flexibility/Fluency
    - Verbal/Figural Fluency
  - Problem solving/reasoning:
    - WCST-64
    - DKEFS: 20 Questions
    - Tower of London
    - DKEFS-Tower Test
  - Inhibition/interference
    - ?Stroop Color-Word Interference

• **Pediatrics**
  - Sequencing/Set-shifting
    - Trail Making Test, Part B
    - WCST-64
    - DKEFS: Trail Making
  - Flexibility/Fluency
    - Verbal/Figural Fluency
  - Problem solving/reasoning:
    - WCST-64
    - DKEFS: 20 Questions
    - Tower of London
    - DKEFS-Tower Test
  - Inhibition/interference
    - ?Stroop Color-Word Interference Trial
  - General/Inhibition/Personality
    - Behavior Rating Inventory of Executive Function (BRIEF)
Executive: Sequencing
Executive Functions: Reasoning

• Deductive reasoning
  • How is coal and wood alike?
  • How is bacteria and humans alike?
• Inductive reasoning
  • 5 different uses for a brick
Language Tests

- **Includes Expressive/Receptive Language**
  - Children/adolescents
    - ADD Reading Comprehension, spelling, writing

- **Why given?**
  - Adults
    - Indicator of lateralization/localization
    - Used to predict language outcome for surgical patients
    - Used to predict seizure freedom in limited, nonlesional cases
  - Pediatrics
    - Indicator for lateralization/localization
    - Used in diagnosis of learning disorder
    - Predictive of language outcome for surgical patients
# Language Tests

## Adults

- **Expressive**
  - Controlled Oral Word Association Test (COWAT) of the Multilingual Aphasia Exam
  - Delis-Kaplan Verbal Fluency
  - Semantic verbal fluency Test
  - Boston Naming Test (BNT)
  - Columbia Auditory Naming Test

- **Comprehension**
  - Peabody Picture Vocabulary Test-4th Ed. (PPVT-IV)
  - Token Test

- **Phonetics**
  - Comprehensive Test of Phonological Processing-2nd Ed. (CTOPP-2)

## Pediatrics

- **Expressive**
  - COWAT - BNT
  - DKEFS – Verbal Fluency
  - Semantic Verbal Fluency Test
  - NEPSY-II Word Generation
  - Expressive One Word Picture Vocabulary Test

- **Comprehension**
  - PPVT-IV - Token Test
  - Receptive One Word Picture Vocabulary Test
  - NEPSY-II Comp. of Instructions

- **Phonetics/combined**
  - CTOPP-2
  - Clinical Evaluation of Language Fundamentals-4th Ed. (CLEF-4)
Object naming:
Easy Item
Object Naming:
Difficult Item
Verbal Fluency

Letter (phonemic) Fluency

- Words you can think of starting with letter…. F, A, S

Semantic (category) fluency

- Name as many different … Animals….as you can
Visuoperceptual/Constructional

- Includes Visuoperceptual, Visuospatial, and Visuoconstructional functions
- Why given?
  - Adults
    - Indicator of lateralization/localization
  - Pediatrics
    - Indicator for lateralization/localization
    - Used in diagnosis of learning disorder
      - Mathematics Deficits due to visual inattention
Visuoperceptual/Constructional Tests

**Adults**
- Wechsler Block Design Subtest
- Rey Osterrieth-Complex Figure (ROCFT)
- Benton Line Orientation Test
- Hooper Visual Organization Test

**Pediatrics**
- Wechsler Block Design
- Wechsler Perceptual Reasoning (Organization) Index
- Add Matrix Reasoning/Picture Completion
- ROCFT
- NEPSY-II Pattern Construction
- Wide Range Assessment of Visual Motor Abilities (WRAVMA)
- Hooper Visual Organization Test
- Benton Line Orientation Test
Memory Assessments

- Memory and Learning – comprehensive
  - Wechsler Memory Scale – III / IV
  - Wide Range Asses. of Learning and Memory - 2

- Auditory (verbal) learning and memory
  - Auditory Verbal Learning Tests
  - Story Memory
  - Verbal Paired Associates

- Visual (non-verbal) memory
  - Complex Figure Test (ROCFT, ACFT, RBANS)
  - Tactual Performance Test (Memory & Location)
  - Warrington Face Memory
  - Visual Paired Associates
Memory Tests

- **Declarative Memory Assessment and Learning**
- **Assessment of Verbal (Auditory) Memory**
  - Immediate (short-term) Memory/Learning
    - Exceeds Auditory/Spatial span and requires mesial temporal function
  - Delayed (long-term) Memory
    - Recall of material after 20-40 minutes
- **Why given?**
Memory Tests

• Why given?
  – Adults
    • Indicator of lateralization/localization
    • **Used to predict memory outcome for surgical patients**
    • Predict seizure freedom in limited, nonlesional cases
    • Diagnosis of Dementia
    • Determination of Capacity
  – Pediatrics
    • Indicator for lateralization/localization
    • Predict memory outcome for surgical patients
    • Predictive of seizure freedom in limited, nonlesional cases
    • Diagnosis and treatment planning
Memory Tests

- **Adults**
  - Verbal (Auditory) Memory
    - Rey Auditory Verbal Learning Test (RAVLT)
    - California Verbal Learning Test-2\textsuperscript{nd} Ed (CVLT-II)
    - Hopkins Verbal Learning Test-Revised (HVLTR)
    - Wechsler Memory Scale-4\textsuperscript{th} Ed.
      - Logical Memory
      - Word Pairs
  - Visual Memory
    - ROCFT recall
    - Wechsler Memory Scale-4\textsuperscript{th} Ed.
      - Visual Reproduction
      - Design Memory

- **Pediatrics**
  - Verbal (Auditory) Memory
    - California Verbal Learning Test – Children’s Version (CVLT-C)
    - Rey Auditory Verbal Learning Test (RAVLT)
    - Child Memory Scale
      - Story Memory
      - Word-Pairs
    - Wide Range Assessment of Memory and Learning – 2\textsuperscript{nd} Ed. (WRAML-2)
  - Visual Memory
    - Rey Osterrieth Complex Figure
    - Child Memory Scale (CMS)
      - Faces
      - Spatial Locations
    - WRAML-2
Verbal Memory

- Bat
- Cannon
- Ray
- Floor
- Orange
- Mayor
- Bus
- Play
- Corner
- Salad
- Lever
- square
Visual Memory

• Memory and Learning – comprehensive
  – Wechsler Memory Scale – III / IV
  – Wide Range Asses. of Learning and Memory - 2

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  – Visual Paired Associates
Mood/Affect and Quality of Life

• Includes Depression/anxiety, psychosis/delusions, and quality of life

• Why given?
  – Adults
    • Diagnosis
      – 30-35% with depression D/O
      – 20-25% with anxiety D/O
    • Treatment Planning
    • Predict outcome/adjustment from surgery
  – Pediatrics
    • Diagnosis
    • Treatment planning/family adjustment
    • Predict adjustment from treatment
Mood/Affect and Quality of Life

**Adults**
- Beck Depression Inventory-2nd Ed (BDI-2)
- Beck Anxiety Inventory (BAI)
- Minnesota Multiphasic Personality Inventory-2nd Ed. (MMPI-2)
- Quality of Life in Epilepsy-31 (QOLIE-31) (also -10, -89)
- Liverpool Battery
- Vineland Adaptive Behavior Scales-2nd Ed. (VABS-II)
- Adaptive Behavior Assessment System-2nd Ed. (ABAS-II)
- Sales of Independent Behavior-Revised (SIB-R)

**Pediatrics**
- Achenbach Child Behavior Checklist (CBCL)
- Achenbach Youth Self Report (YSR)
- Child Depression Inventory-2nd Ed. (CDI-II)
- Beck Youth Inventory-2nd Ed. (BYI-2)
- Revised Children’s Manifest Anxiety Scale-2nd Ed. (RCMAS-2)
- Minnesota Multiphasic Personality Inventory-Adolescent (MMPI-A)
- VABS-II
- ABAS-II
- SIB-R
- Child Health Questionnaire
- Quality of Life in Childhood Epilepsy
- Quality of Life in Epilepsy Inv for Adolescents
- Health Related Quality of Life (HRQOL)
- Impact Childhood Neurologic Disability Scale
- Pediatric Quality of Life Inventory
Academic Achievement

• Not core assessment
• Required for evaluation of learning disabilities/school accommodations
• Includes assessment of reading comp, spelling, math
  – Adults
    • Diagnosis
    • Treatment Planning/rehabilitation interventions
  – Pediatrics
    • Diagnosis of LD
    • Treatment planning/school accommodations
    • Can be impaired prior to first recognized seizure
Academic Achievement

- **Adults**
  - Wechsler Individual Achievement Test-3rd Ed. (WIAT-III)
  - Wide Range Achievement Test-4th Ed. (WRAT-4)
  - Woodcock Johnson Tests of Achievement-3rd Ed. (WJ-III)

- **Pediatrics**
  - Wechsler Individual Achievement Test-3rd Ed. (WIAT-III)
  - Wide Range Achievement Test-4th Ed. (WRAT-4)
  - WJ-III)
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• Neuropsychological Assessment in Epilepsy
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  – Common Data Elements
    • General Cognitive/IQ
    • Attention/executive
    • Language
    • Memory
    • Memory
    • Visuoperceptual/constructional
    • Motor
    • Mood

• Evidence-based Medicine For Neuropsychology in Epilepsy
  • Predict memory/language outcome
  • Predict Seizure outcome

• Cognitive/behavioral effects of AEDs
Evidence Based Practice: Epilepsy is a progressive disease

- 20-30% of patients with localization related medication refractory epilepsy decline in cognitive function over 4-7 years.
- Another 20-30% do not exhibit practice effects, suggesting mild declines.
- Predictors of decline:
  - Structural lesion on MRI or Structural atrophy (OR=10)
  - Low IQ (OR=5)
  - Duration of epilepsy (OR=4)
  - Age – older age worse (OR=2)
  - Education (more education decreases risk) (OR=2)
Presurgical Neuropsychology: Predicting Cognitive Outcome from Surgical Treatment

- Side of surgery
- Presence of unilateral mesial temporal lobe sclerosis (MTS) on MRI
- Hippocampal volumetric analysis
- Age of epilepsy onset
- Duration of Epilepsy
- Neuropsychological Preoperative memory scores
- Wada Test findings
  - Contralateral Wada test Inj.
EBM for Predicting Post-surgical outcome: Memory

- **Predictors**
  - Pre-surgical memory scores ≥ 90 (≥25th %)
    - Memory scores 90+ 4 times more likely have Verbal memory decline (OR=3.9)
  - Mesial temporal sclerosis ipsilateral only
  - Age of seizure onset (later age = more risk)
  - Duration of seizures (shorter = more risk)
  - Side of surgery (language dom. ↑ risk)
  - Wada test scores (contralateral inj.=intact)
  - fMRI findings
Predicting postoperative memory decline in temporal lobectomy

- **Verbal memory loss** (by RCI) is
  - twice as high among Left ATLs (44%) than Right ATLs (20%).

- **Visual memory loss** (by RCI) is
  - Similar after both L (21%) & R ATL (23%)

- **Chelune et al., 1991 (WMS-R)**
  - 67% ≥ Avg Memory declined
  - 44% - Low-Avg declined
  - 12% ≤ Borderline declined

- **Prediction of Memory Decline**
  - The better preoperative memory, the greater the postoperative decline.
Prediction of verbal memory loss by WMS-R & presence of hippocampal atrophy (by MRI volumetrics)  
(Chelune & Najm, 2001)

<table>
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<th>Left ATL</th>
<th>Odds ratio: Case Controls</th>
<th>Odds ratio: Between Groups</th>
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<tr>
<td><strong>WMS-R VMI ≥ 90</strong></td>
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<td>Left ATL</td>
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<td>WMS-R VMI ≥ 90</td>
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<td>Right ATL</td>
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<td>WMS-R VMI ≥ 90</td>
<td>1.62</td>
<td>1.14</td>
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<tr>
<td>WMS-R VMI ≤ 90</td>
<td>1.42</td>
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Intracarotid procedure (Wada test)

- Injection of anesthetic agent (methohexital or sodium amytal) into common carotid arteries
  - De-affernate mesial temporal lobe structures
  - Test language (expressive/receptive)
  - Test memory (8 memory items)
    - Spontaneous recall and recognition from foils
Wada test: Predictive Value

• **Seizure side/seizure freedom**
  - Wada’s memory asymmetry predicted *seizure laterality* in both TL and extra-temporal lobe seizures (Lee et al., 2002)
  - Memory score asymmetries consistent with side of seizure onset were sig. related to *seizure freedom* (Lee et al., 2003)
  - Patients with NO memory asymmetry or asymmetry disparate from side of surgery were less likely to be seizure free
  - Wada results NOT concordant with EEG findings may implicate increase risk for poor seizure outcome

• **Memory**
  - Best use is to predict amnestic syndrome for patients with neuropsychological study memory deficits.
  - Functional adequacy of ipsilateral MTL predictive of post-operative memory change
  - Intact contralateral MTL predictive if patient at risk for amnestic syndrome
Predicting Seizure freedom from Cognitive Function

• Cognition as a predictor of sz outcome in children
  – IQ
    • Highly lateralized IQ (VIQ-PIQ scores >15 points) predictive of seizure laterality in children with left hemisphere language
    • More likely to be seizure free if VIQ/PIQ highly lateralized in correct direction
  – Memory
    • More likely to be seizure free if memory lateralized to side of surgery.
  – Wada test
    • Wada memory asymmetry predicted seizure laterality in both TL and extra-temporal lobe focal seizures (Lee et al., 2002)
    • Memory score asymmetries consistent with side of seizure onset were sig. related to seizure freedom (Lee et al., 2003)
Increased risk for verbal memory loss have:

(Stroup, Langfit, et al., 2003)

- Dominant temporal lobectomy (left ATL)
- Absence of ipsilateral (to seizure focus) mesial temporal lobe sclerosis
- Normal preoperative performance on 2 immediate memory tests
- Normal preoperative performance on 2 test of delayed memory
- Normal Wada memory after contralateral (to seizure focus) amobarbital injection
EBM for Predicting Post-surgical outcome: Language

Predictors

- Dominant hemisphere (Left) resection
  - About 1/3 of patients experience reliable decline
- Pre-surgical naming scores
  - Lower score less likely to decline
- Age of seizure onset
  - Early age of seizure onset less likely to decline
- Duration of seizures
- Presence of structural pathology
- ? Extent of superior temporal gyri resection
Naming Errors and Stimulation of the Superior Temporal Gyrus

Source: Devinsky et al. (1993)
Post-surgical outcome: Quality of Life

Predictors
- Seizure freedom (~70% of patients)
- Less Neuropsychological comorbidity
- Pre-surgical psychiatric symptoms
- Social/family support
- Psychological/coping mechanisms
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• Conclusions – Learning Objective Summary
Conclusions: Key Points

• Epilepsy is associated with neuropsychologic and psychiatric comorbidity
• Cognitive impairment due to complex interaction of non-independent variables
  – Cognitive deficits and psychiatric symptoms can be present before 1\textsuperscript{st} recognized seizure
  – Cognitive deficits present at first onset of unprovoked seizure
  – Structural deficits not present with cognitive impairment
Conclusions: Key Points

• Neuropsychological variables best predictor of memory outcome for patients having ATL
  – Patients with intact memory = greater loss
• Neuropsychological confrontation naming predict post-operative naming deficits
  – Higher BNT score, increased risk for decline
• Neuropsychological variables can assist predict seizure freedom in nonlesional cases when strongly lateralizing.
Questions