Precision Neuropsychological Assessment and Treatment in the Neurosurgical Context

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Disclosures

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Aims of Presentation

- Epilepsy surgery setting as a model environment for improving structure-function brain knowledge and developing new tests
  - Bozeman Consortium – Forerunner of NNN?
  - Unique tools and opportunities in epilepsy setting.
- Example of how the precision of surgery can challenge existing models of brain function.
- Examples of how new tests can open new windows on function and lead to improvements in surgery and general assessment.

Bozeman Consortium Members

- William Barr, *Long Island Jewish Hospital*
- Gordon Chelune, *Cleveland Clinic Foundation*
- Bruce Hermann, *Baptist Memorial Hospital*
- David Loring, *Medical College of Georgia*
- Kenneth Perrine, *New York University*
- Esther Strauss, *University of Victoria*
- Max Trenerry, *Mayo Clinic, Rochester*
- Mike Westerveld, *Yale University*

The work of these investigators represents the power of aggregating large data samples.

18 Peer Reviewed Articles (1995-2003)

- Barr and colleagues (1997) Sensitivity of figural fluency tests to right temporal lobe dysfunction
- Chelune and colleagues (1998) Relationship of IQ to seizure outcome after temporal lobectomy
- Hermann, Connell, Barr, and Wyler (1995) Sensitivity of the Warrington Memory Test to lateralized temporal lobe epilepsy
- Hermann, Trenerry, and Colligan (1996) Contributors to depression in TLE
- Hermann and colleagues (1999) Relationship of surgical approach in left ATL to post-operative naming outcomes
- Loring and colleagues (1997) Memory stimulus type and Wada memory outcomes
- Loring and colleagues (1999) “Crowding” associated with nonspace occupying lesions
- Loring, Hermann, Lee, Drane, and Meador (2000) Sensitivity of the Memory Assessment Scales to lateralized temporal lobe epilepsy
- Loring and colleagues (2008) Sensitivity of common naming and verbal memory measures to left TLE

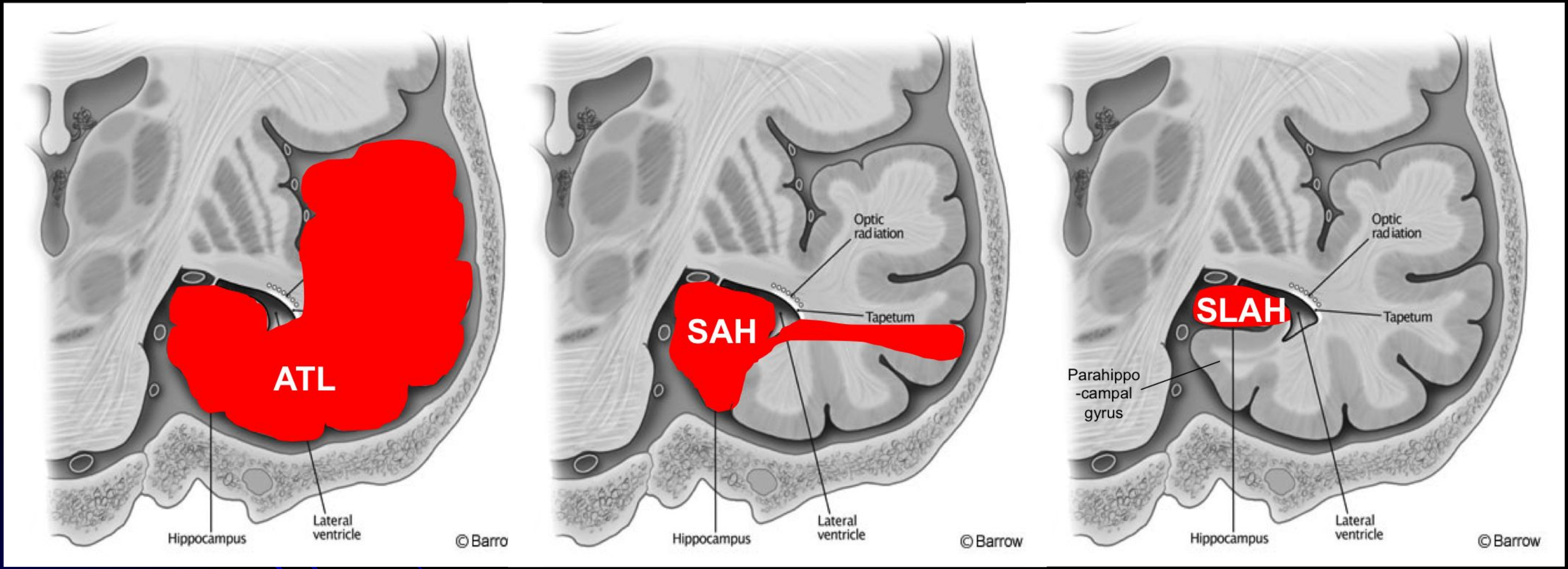
18 Peer Reviewed Articles (1995-2003)

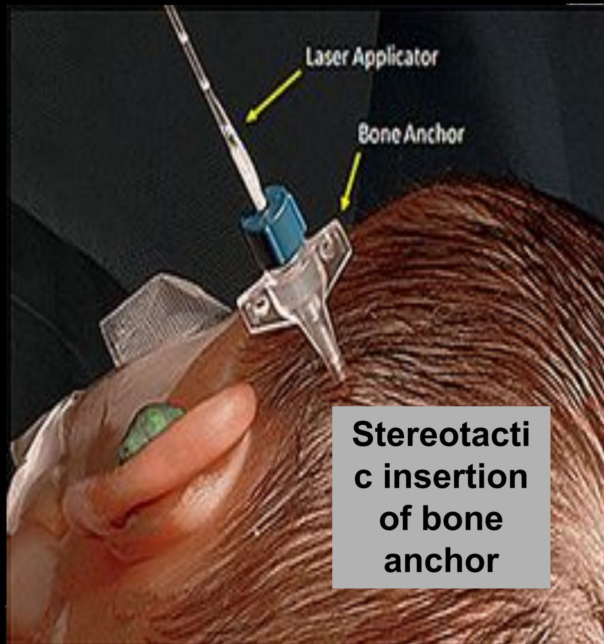
- Perrine, Hermann, and colleagues (1995) Relationship of quality of life to neuropsychological performance in epilepsy
- Perrine, Westerveld, and colleagues (1995) Relationship of Wada memory asymmetries predict post-operative seizure outcome
- Strauss and colleagues (1995) Factors are related to impaired neuropsychological profiles in epilepsy
- Strauss and colleagues (1997) Differential rates of age of seizure onset between sexes and between hemispheres
- Strauss and colleagues (2000) Category-specific naming risks associated with left ATL
- Trenerry and colleagues (1996) MMPI profiles differences between left and right TLE patients and differential changes following ATL
- Westerveld and colleagues (2000) Cognitive outcomes in pediatric ATL
- Wilde and colleagues (2001) Sensitivity of WMS-III index discrepancies in patients with TLE
- Wilde and colleagues (2003) Confirmatory factor analysis of WMS-III in patients with TLE

Unique tools and opportunities in the epilepsy surgery setting

- Novel minimally-invasive surgical techniques allow us to electrically or surgically perturb neural networks in a more selectively precise manner.
- Cortico-cortical evoked potentials/stereo-electroencephalography (SEEG) allow us to chart connectivity and improve temporal precision of measurement.
- Patients can be studied precisely before and after surgery.

Comparison of SLAH and Open Resection Approaches

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Stereotactic
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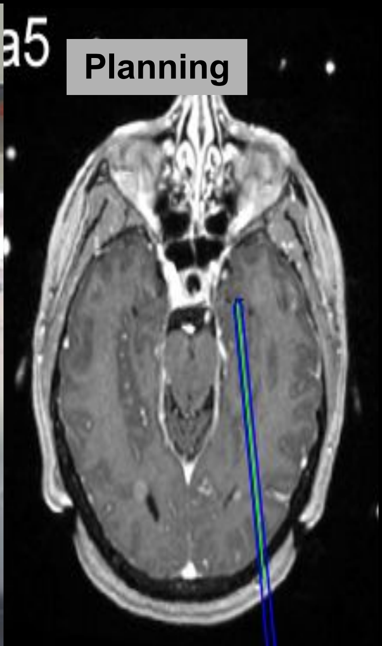
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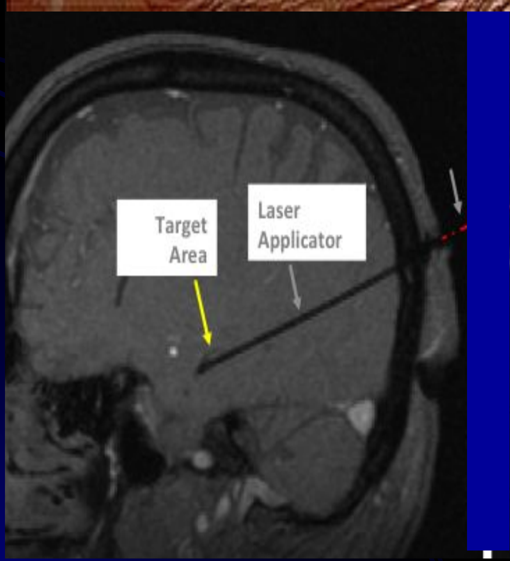
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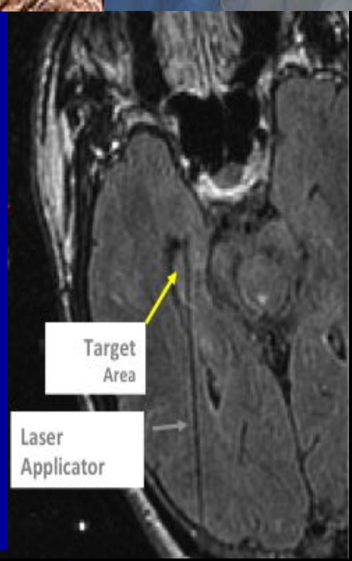
Target
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Applicator

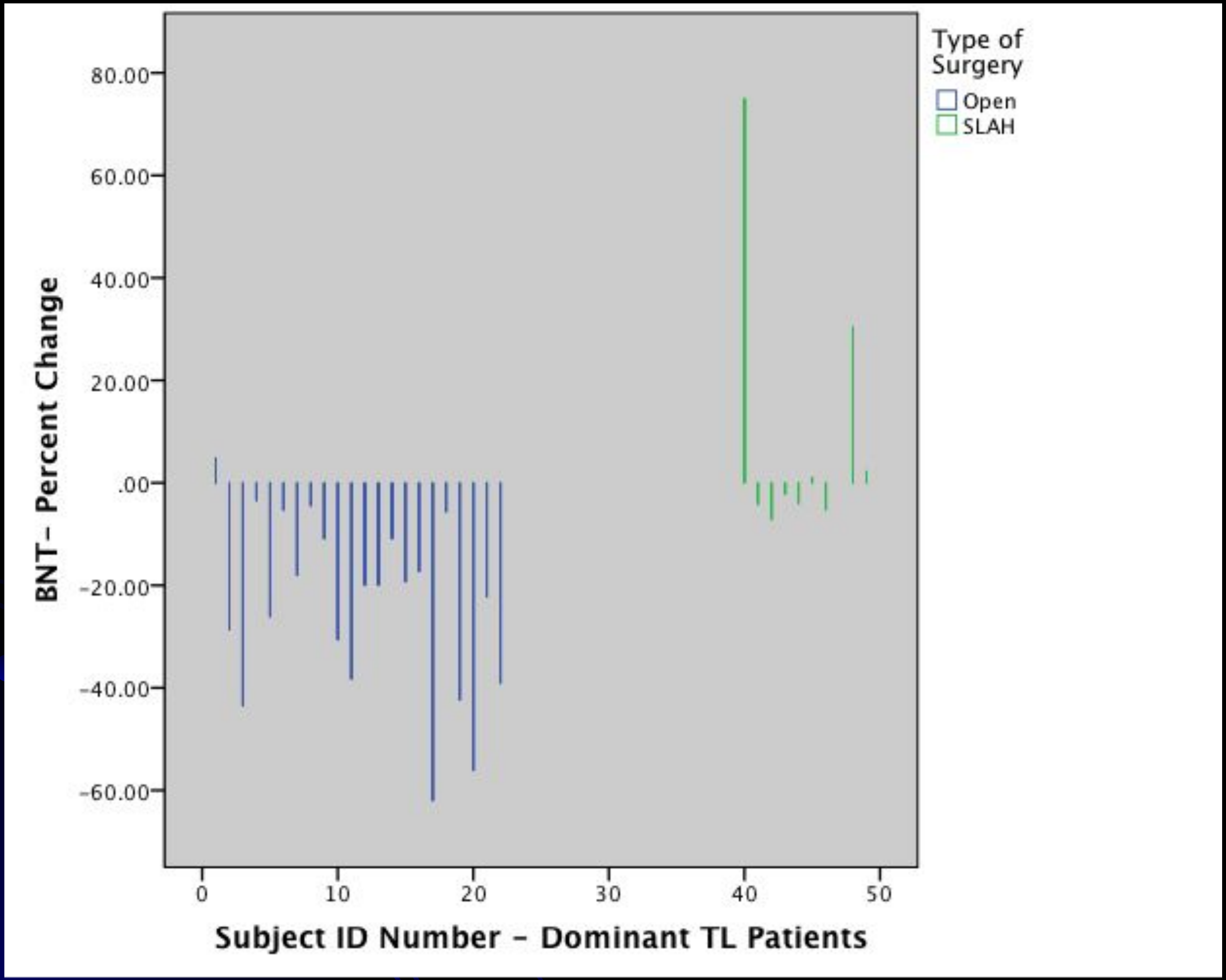
Needs for Clinical Care and Practice

- Better Targeting/localization of seizures and improved knowledge of structure-function relationships will be necessary to use targeted resections/ablations to their optimal potential (decreasing cognitive and behavioral morbidity and better prediction of seizure outcome).

- Novel paradigms need to be developed and implemented to study cognition in a more complex manner that takes network interactions seriously in a more “real-world” manner (e.g., Multimodal learning of new information that requires integration of spatial context and preexisting knowledge; prospective learning).

Examples of how the precision of surgery can challenge existing models of brain function

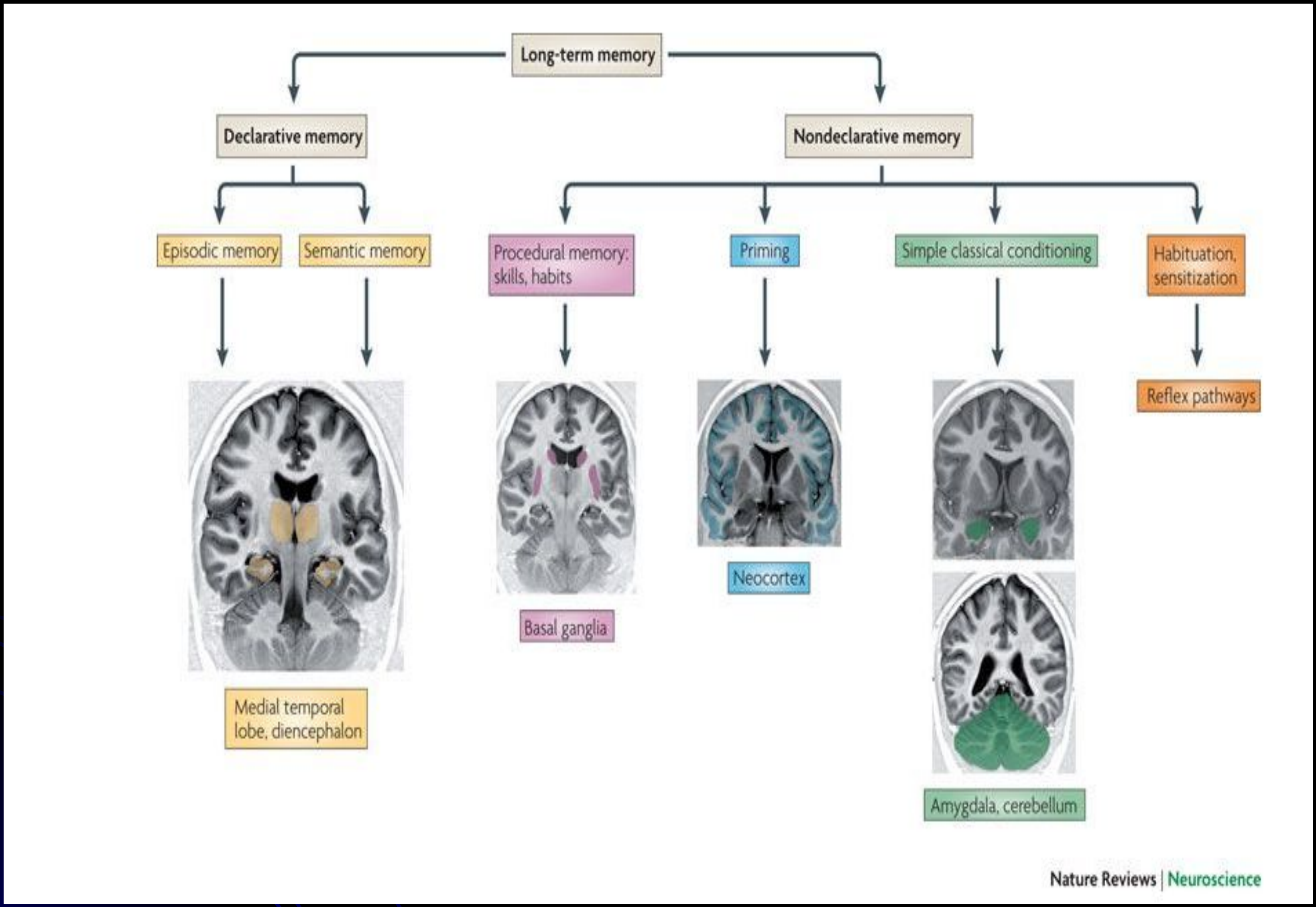
Post-Surgical Change in Man-Made Object Naming (Boston Naming Test) Performance by Surgery Type



Drane et al. (2015) *Epilepsia*.

We have used laser ablation technique to demonstrate that hippocampus is not needed for retrieving names of man-made objects of famous persons (or for recognition of these items

Note. BNT = Boston Naming Test; SLAH = stereotactic laser amygdalohippocampotomy; open = open resection; TL = Temporal Lobe.



Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature Reviews Neuroscience*, *11*, 523-532.

Verbal Memory Outcome with SLAH

Hippocampal ablation not leading to significant memory decline in most cases as opposed to open resection procedures

TABLE 2. Verbal Memory Outcomes

	RAVLT–Learning		RAVLT–Delayed Recall	
	Pre-SLAH	Post-SLAH	Pre-SLAH	Post-SLAH
All subjects, n = 49	41.8 ± 10.8 (14–65)	41.9 ± 11.6 (11–59)	5.9 ± 3.9 (0–15)	6.5 ± 4.1 (0–14)
Language dominant hemisphere SLAH, n = 20	37.4 ± 10.7 (14–62)	35.3 ± 12.7 (11–56)	4.6 ± 3.7 (0–13)	4.2 ± 3.4 (1–12)
Nondominant hemisphere SLAH, n = 29	44.9 ± 10.0 (33–65)	46.6 ± 8.3 (22–59)	6.6 ± 3.9 (1–15)[a]	8.2 ± 3.7 (0–14)[a]

Scores are presented as mean ± standard deviation (range).

[a]Scores differed significantly across pre- and postsurgical ablation time points ($p < 0.05$).

RAVLT = Rey Auditory Verbal Learning Test; SLAH = stereotactic laser amygdalohippocampotomy.

Gross, R. E., Stern, M. A., Willie, J. T., Fasano, R. E., Saindane, A. M., Soares, B. P., Pedersen, N. P., & Drane, D. L. (2018). Stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Annals of Neurology*, *83*, 575-587.

SLAH vs. Open Resection – Verbal Memory Outcome

Table 1. Demographic, Disease-Related Variables, Surgical Characteristics, and Test Performances by Surgical Group.

	Standard Open Resections		Stereotactic Laser Amygdalohippocampotomy		Significance
Side of Surgery	19 Dominant /21 Nondominant		19 Dominant/21 Nondominant		*n.s.*
	Dominant	Nondominant	Dominant	Nondominant	
	X *SD* (Range)	*X* *SD* (Range)	*X* *SD* (Range)	*X* *SD* (Range)	
Age (years)	36.9 12.4 (21 to 59)	39.2 10.8 (22 to 58)	39.3 17.0 (16 to 67)	40.7 14.3 (21 to 64)	*n.s.*
Education (years)	12.4^{I} 2.2 (9 to 18)	15.1^{I} 2.4 (9 to 19)	13.4 3.2 (8 to 20 years)	13.9 2.3 (10 to 18)	$F(3, 76)=3.9$, $p<.02$
Age of Onset	21.2 14.2	18.8 12.3	14.6 10.1	18.7 14.9	*n.s.*
MTS	10/19	10/21	14/19	10/21	*n.s.*
RAVLT – 5-Trial Total (Pre)	39.1 11.8	43.8 7.8	38.0 10.6	43.9 9.8	*n.s.*
RAVLT – 5 Trial Total (Post)	$30.1^{\alpha\kappa\delta}$ 7.1	$45.9^{\alpha\beta}$ 9.2	$36.7^{\kappa\beta\gamma}$ 10.4	$46.5^{\delta\gamma}$ 8.1	$F(3, 76)=15.1$, $p<.001$
RAVLT – Delay (Pre)	6.2 4.2	7.2 4.0	4.8 3.7	6.3 4.0	*n.s.*
RAVLT – Delay (Post)	*2.6*$^{\Sigma\nu}$ 2.3	*7.3*$^{\Sigma\kappa}$ 4.9	$4.4^{\kappa o}$ 3.3	*8.4*$^{\nu o}$ 3.7	$F(3, 76)=10.1$, $p<.001$

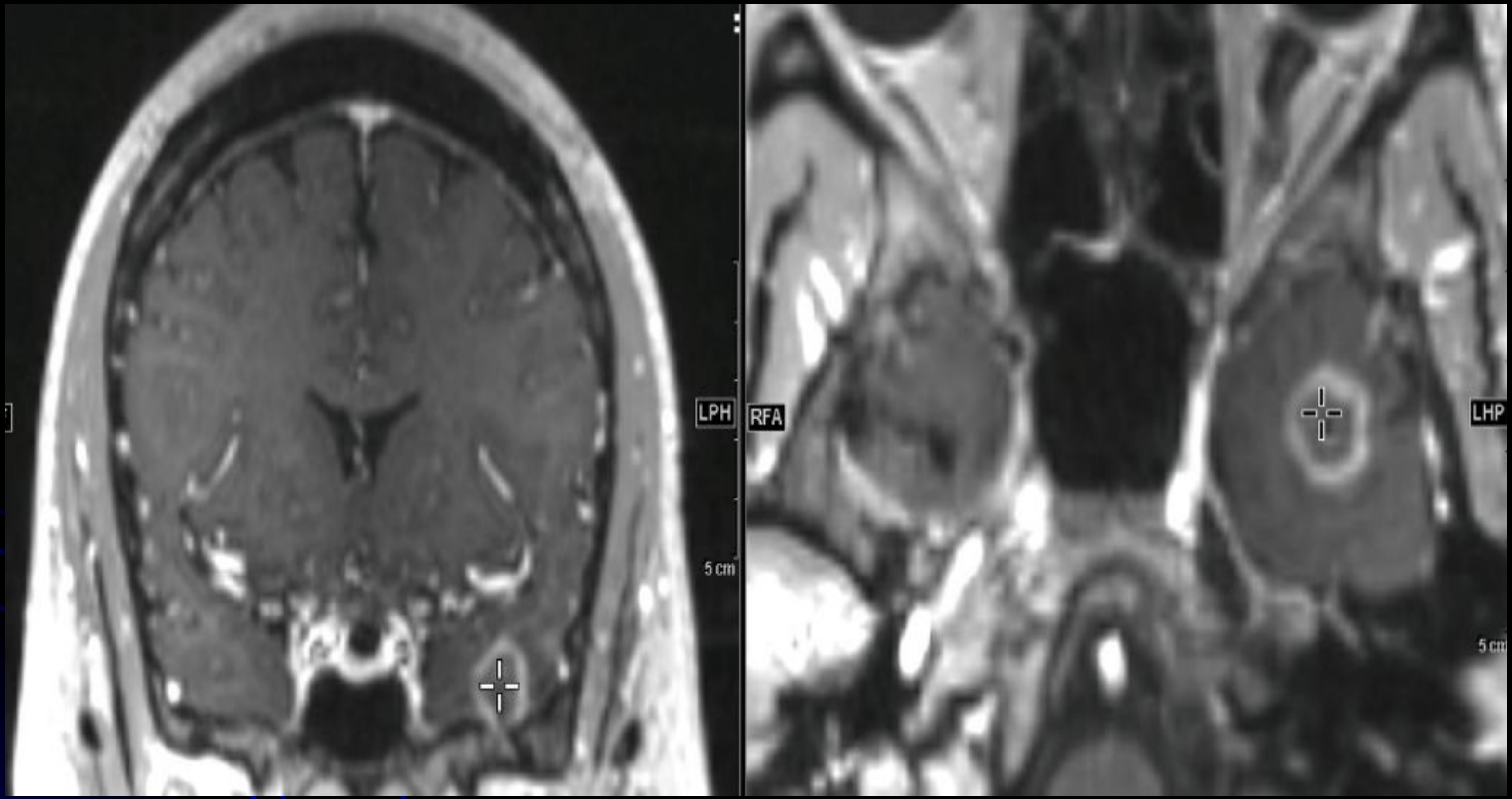
Deficits Still Occur if We Destroy Functional Tissue With Any Method

- Selective ablation of regions not traditionally destroyed in isolation during surgery is leading to surprising insights into brain function.

Examples of Focal Surgical Procedures Leading to Unexpected Cognitive and Emotional Consequences

Led to selective decline in famous face naming and improvement in common object naming; Open resection would have likely led to general decline in both object types. RAVLT declined significantly as well (list learning) and associative learning (> 2SD)

Stereotactic Laser Ablation of Basal Temporal Lobe Lesion



Stereotactic Laser Ablation of Basal Temporal Lobe Lesion

Areas of Decline	Areas of Stability/Improvement
Naming of Famous and Familiar Persons Significantly Declined	Naming of Animals and Man-Made Objects Unchanged
Verbal associational learning and list learning significantly declined	Verbal contextual learning (gist learning) unchanged
Emergence of novel OCD traits	Visual Memory was stable or improved

Notes. OCD = Obsessive Compulsive Disorder

Novel Conclusions - Memory

- Memory is supported by several sub-systems which are supported by neural circuitry that involves multiple brain regions and pathways (medial TL, basal forebrain, diencephalon).

- While the hippocampus and amygdala are involved in memory, animal data, re-appraisal of case HM, and lesion analysis made possible by minimally invasive procedures suggest that broader aspects of the medial TL are perhaps equally or even more critical for functional memory.

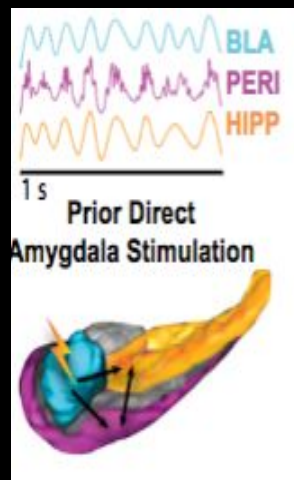
- More attention needs to be paid to the contribution to memory of the lateral TL region/basal temporal language area.

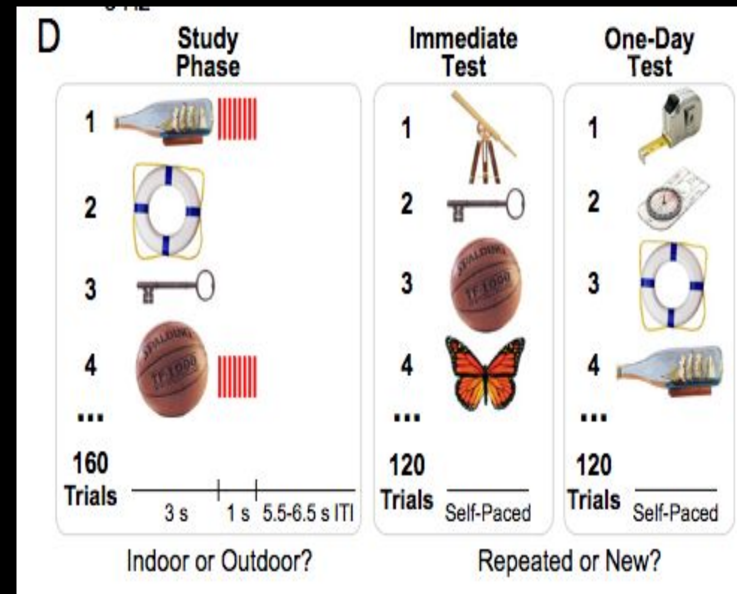
- Coordinated use of neuroimaging, cortical-cortico evoked potentials and stimulation paradigms, and novel cognitive and emotional paradigms will potentially lead to better understanding of memory substrates.

Direct electrical stimulation of the amygdala enhances declarative memory in humans

Cory S. Inman[a,1], Joseph R. Manns[b,1], Kelly R. Bijanki[a], David I. Bass[c], Stephan Hamann[b], Daniel L. Drane[d], Rebecca E. Fasano[d], Christopher K. Kovach[e], Robert E. Gross[a,d,f], and Jon T. Willie[a,d,2]

Stimulation of the baso-lateral amygdala during encoding of novel objects led to better recall of such objects the following day.





"This reappearance of theta-modulated gamma oscillations in the MTL during retrieval could possibly indicate a reactivation of an amygdala-induced network state or could reflect the overall importance of theta and gamma oscillations for appropriate medial temporal lobe function.

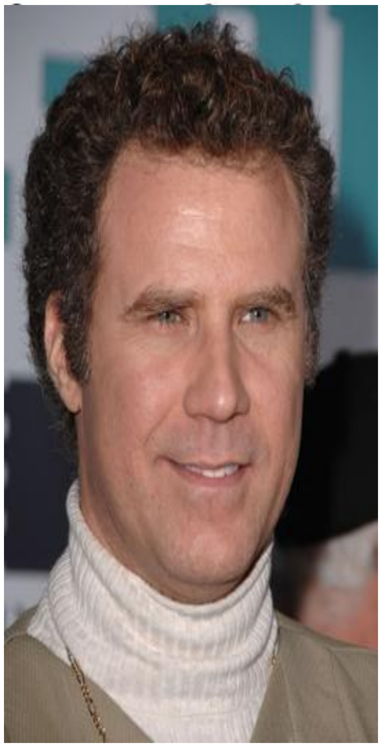
Inman et al. (2018). PNAS.

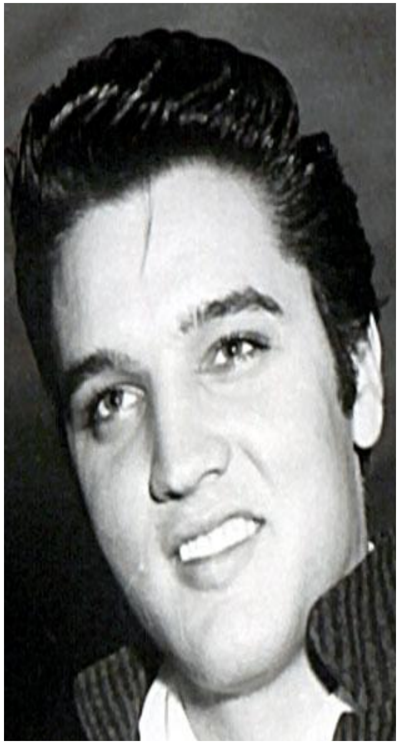
Future Directions

Developing New Tests and Paradigms to explore novel theories/insights arising in this precision surgical context

Famous face identification in temporal lobe epilepsy: Support for a multimodal integration model of semantic memory

Daniel L. Drane[a,b,*], Jeffrey G. Ojemann[c,d], Vaishali Phatak[b], David W. Loring[a], Robert E. Gross[e], Adam O. Hebb[c], Daniel L. Silbergeld[c], John W. Miller[b], Natalie L. Voets[f], Amit M. Saindane[g], Lawrence Barsalou[h], Kimford J. Meador[a], George A. Ojemann[c] and Daniel Tranel[i]

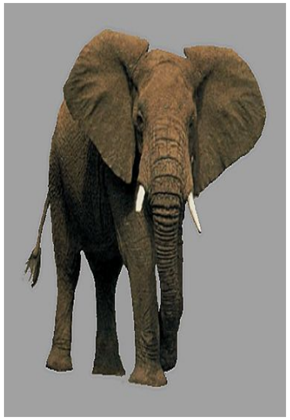


Cortex 49 (2013) 1648-1667

Category-specific naming and recognition deficits in temporal lobe epilepsy surgical patients

Daniel L. Drane[a,b,*], George A. Ojemann[b,c], Elizabeth Aylward[d], Jeffrey G. Ojemann[b,c], L. Clark Johnson[e], Daniel L. Silbergeld[b,c], John W. Miller[a,b], Daniel Tranel[f]



Neuropsychologia 46 (2008) 1242-1255

Emory Semantic Fluency Paradigm

- We have developed multiple common and proper noun fluency measures.
- All involve standard and cued applications.
- Have been used to disentangle frontal lobe vs. temporal lobe contributions to semantic retrieval.
- Employed FDA trial of laser ablation and FATES study of fMRI of memory prediction in epilepsy.

Drane, D. L., Lee, G. P., Cech, H., Huthwaite, J. S., Ojemann, G. A., Ojemann, J. G., Loring, D. W., & Meador, K. J. (2006). Structured cueing on a semantic fluency task differentiates patients with temporal versus frontal lobe seizure onset. *Epilepsy and Behavior*, *9*, 339-344

Iudicello, J. E., Kellogg, E. J., Weber, E., Smith, C. E., Grant, I., Drane, D. L., Woods, S. P., & The HIV Neurobehavioral Research Program (HNRP) Group. (2012). Semantic cueing improves category verbal fluency in persons living with HIV infection. *Journal of Neuropsychiatry and Clinical Neurosciences, 24 (2)*, 183-190.

Wolff, L., Ortiz-Hernandez, S., Beevers, S., Drane, D. L., & Benge, J. F. (2019). A pilot study of the relationship between action generation and apathy in Parkinson's disease. *Journal of the International Neuropsychological Society*.

- **National Neuropsychology Network**

- Gathering large amounts of neuropsychometric data across multiple patient and healthy control cohorts.
- Using psychometric approaches, such as item response theory, to enable linking procedures that can place different measures on common scales.
- Adaptive testing technologies to dramatically increase testing efficiency (e.g., computerized adaptive testing).
- Examination of differential item functioning (DIF) to detect measures that behave differently in different groups.
- Building a platform of “classic tests” upon which to build novel measures.

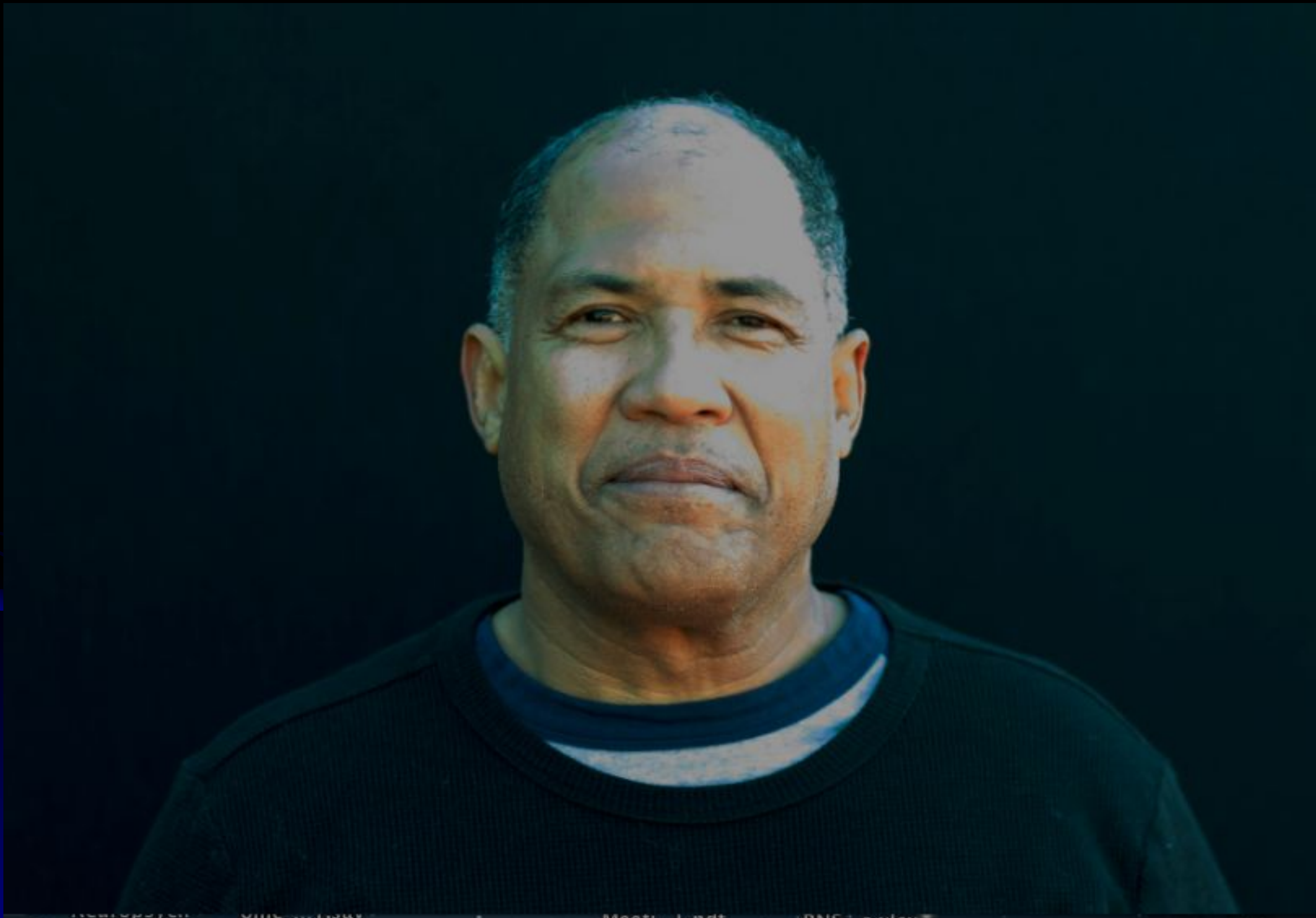
Emory Multimodal Learning Test

Daniel L. Drane and Keith Adams (SpinVFX)

- New Generation Task – Designed to study novel declarative learning and recall using “real-world” videoclips of actors/actresses portraying common life events in a fictional town.
- Allows for prospective face-name and voice-name learning, a high level of control over background elements (incidental learning and distractors), and the integration of information including auditory and visual input and semantic/linguistic information.
- Funded by Children’s Hospital of Atlanta/Goizueta Foundation

Charlie Stewart at Cletus Jones Park in Vincent Falls


Cypress Valley
Vincent Falls
Smithtown
Lincoln Park High School
Lake Jackson
Grovetown
Grovetown Recreation Center
Waldorf Apartment Complex
Vincent Falls
Jones Park
Little Bingham
Garden City

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Methods of Assessment - Emory Multimodal Learning Test

- Free recall of specified content (e.g., names of primary story tellers, names mentioned (famous and nonfamous), names of places mentioned (famous and nonfamous), settings
- Recognition of faces (presented as head shots) and voices (neutral phrases). We would also query the subjects ability to put names and semantic content with face and voice.
- Recognition of objects, persons, and context.
- Recognition of specific objects with foils that are altered in sensory quality.
- Matching faces, names, etc. to locations.
- Specific Questions – with spontaneous response and multiple choice options.
- Questions about emotional content.
- Spatial recall of map elements
- Executive integration of information across scenes with related elements.

Primary Collaborators on Research Projects Discussed During Presentation

Emory University, Atlanta, Georgia

David Loring, PhD — Robert E. Gross, MD, PhD — Jon Willie, MD, PhD
Amit Saindane, MD — Edward Faught, MD — Gloria Novak, MS
Nigel Pedersen, MD — Bruno Soares, MD — Lawrence Barsalou, PhD
Cory Inman, Ph.D. — Ranliang Hu, MD — Deqiang Qiu, Ph.D.

Oxford University, UK

Natalie Voets, PhD

University of Washington, Seattle, WA

Jeffrey G. Ojemann, MD — George A. Ojemann, MD
Michelle Kim, PhD — Thomas Grabowski, MD
John W. Miller, MD, PhD

SpinVFX (Atlanta)

Keith Adams

University of Iowa College of Medicine, Iowa City, Iowa

Daniel Tranel, PhD

University of Arkansas

Andrew James, PhD

Stanford University School of Medicine

Kimford Meador, MD

Wayne State University

Scott Millis, Ph.D.

Medical University of South Carolina

Leo Bonilha, MD — Ezequiel Gleichgerrcht, MD