Novel Methods of Assessing Memory with Technology: Addressing the Need for New Theory and Measures in the Setting of Minimally Invasive Epilepsy Surgery

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Novel Memory Assessment Methods in Minimally Invasive Epilepsy Surgery

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Abstract. The rise of minimally invasive neurosurgical procedures (e.g., stereotactic laser ablation) coupled with technological advances have revealed gaping holes in cognitive theory and our ability to thoroughly assess such constructs. Being able to create focal surgical destruction zones has revealed a mismatch between existing structure-function theory of the brain and post-surgical results. For example, extant research literature often focuses on the involvement of the medial temporal lobes in memory or the fusiform gyrus in semantic memory/language, yet these highly precise lesional studies are showing theory to often be incomplete or incorrect. In the setting of SLA in epilepsy surgery, some of our worst post-surgical memory outcomes occur when extra-medial TL regions are destroyed rather than medial TL structures. This is likely because cognitive theory has been based on indirect, correlative measures of brain function (e.g., fMRI) or large lesions in the brain resulting from disease or surgery. Additionally, most clinical measures of cognitive and emotional functioning are kept simplistic in nature to allow for the most straightforward interpretation. For example, memory testing is usually done in a sensory domain specific manner (e.g., visual vs. auditory) rather than allowing for integration of memory features (e.g., visual, auditory, semantic, autobiographical, historical being integrated and assessed wholistically). We highlight emerging weaknesses in theory as well as shortcomings in cognitive assessment, and present data to demonstrate how novel tests can be developed using videography, gamification, internet delivery to allow for longer windows of delayed recall, and updated theory to better assess neural network interactions.

Keywords. Memory assessment, telemedicine/virtual assessment, surgical outcome, unity game engine

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1. Introduction

The perfect storm is brewing between the advent of cutting-edge advances in both technology and neuroscientific theory, and promises to unlock new opportunities to study the brain and to advance our options for diagnostic inquiry and treatment alike. Nowhere is this clearer than the neurosurgical setting, where minimally invasive techniques have opened new windows into the structure-function relationships of key cognitive and socio-emotional functions while challenging many long held conceptual and neuroanatomical theories of such constructs.[1,2,3] We will explore some examples of these occurrences from our own work in the epilepsy surgery setting, demonstrating that the field of epilepsy surgery has been severely under-evaluating the construct of memory since its inception 70 years ago, and putting forth our initial efforts to solve some of these problems through novel assessment paradigms and the application of virtual assessment and machine learning algorithms for administration and scoring.

2. Minimally Invasive Surgical Procedures Reveal that Cognitive Theories are Often Wrong

The advent of minimally invasive surgical procedures, such as stereotactic laser amygdalohippocampotomy (SLAH) for carrying out a selected temporal surgery restricted to the amygdalar-hippocampal complex (AHC), has demonstrated that we can do a better job of preserving cognitive function while still conducting surgery for the control of seizures.[2,4] Rather than removing a large portion of the temporal lobe, as is the case in a standard anterior temporal lobectomy (ATL), the neurosurgeon can now restrict surgery using a laser device to just a portion of the AHC. We have demonstrated over the past decade that we can virtually spare all language function and even lessen episodic memory deficits by minimizing the anatomical scope of surgery.[5,6,7,8]

Taking the example of sparing language is a perfect example of the mismatch between scientific theory and the novel revelations resulting from the interface of technology and neuroscience, multiple research articles have suggested a role for the hippocampus is naming ability, and many researchers have suggested that sparing the hippocampus could lead to better language outcomes.[9] There have been at least four lines of research pointing to this hypothesis: (a) associations between presurgical naming scores and hippocampal volumes,[10] (b) hippocampal activation observed during fMRI tasks involving object and face naming,[11] (c) worse naming scores observed in TLE patients with MTS than in those without,[12,13] and (d) observations that naming deficits always occurred when the hippocampus was included in ATLs despite patients undergoing cortical stimulation mapping.[9] All of this supporting research is primarily indirect and correlative rather than a “causal” model. In contrast, our work has shown that actually ablating the language dominant AHC virtually never leads to any form of language dysfunction,[5,6] and that deactivating the hippocampus through a selective posterior cerebral artery Wada procedure likewise leads to no language disruption.[14]

Similarly, with episodic memory, the conventional clinical wisdom has been to spare the hippocampus whenever possible with the goal of preserving memory functioning, with the prevailing thought being that these structures are highly critical to forming new memories. Nevertheless, surgeries sparing the hippocampus have not seemed to preserve memory,[15] and our own work with laser ablation has generally shown a favorable memory outcome when the hippocampus is destroyed. While episodic verbal memory can be affected by a language dominant SLAH, fewer patients tend to decline and the extent of decline appears less in magnitude.[7,8,16] In contrast, some of our worst outcomes on conventional verbal memory measures has occurred following focal surgical lesions created in the fusiform gyrus or the temporal pole.[4] Overall, these findings and much of the animal data on memory suggests that memory is likely dependent on a wide-range of structures that exceed the medial TL region.[17,18,19]

3. Technology and Videography Can Improve Our Ability to Assess Cognition:

While innovative surgical technologies have led to many challenges of long-held structure-function models of cognition, they have also highlighted where there are deficiencies in our current test paradigms. Despite sparing of function on conventional tests following epilepsy surgery, some patients and their families continue to report new onset cognitive problems. We have been carefully interviewing them as part of a long-term outcome research project and have found that there are several areas where our standard tasks are falling woefully short of a complete evaluation. These include an absence of measures designed to explore long-term consolidation of information (i.e., we typically only test recall following a half-hour delay), the emotional contribution to memory, the contextual information of when and where the information was learned, among other constructs. We would like to spend the remainder of this brief review, highlighting how technology may overcome these glaring absences in our assessment armamentarium.

Learning new information prospectively has rarely ever been investigated systematically in any age group, though the consequences of deficits in prospective learning are likely to be much more severe than losing access to stored knowledge and information. Our group has demonstrated that language dominant open resections lead to greatly diminished ability to recall names of famous persons, and that right TL open resections diminish one's ability to recognize such individuals or to recognize familiar landmarks and buildings.[20,21] We have speculated that patients with these deficits, both left and right TL resection patients, will have difficulty putting information with faces or locations albeit for different mechanistic reasons. Such deficits have been reported in the research literature by patients, and are particularly troubling,[22,23] as one would assume that the effects of these deficits would compound with each passing year (i.e., more and more information comes along that such individuals cannot learn), and this leads to greater mental health issues and life limitations.

Furthermore, assessing the multimodal integration of information, such as combining sensory and motor input with semantic/linguistic concepts and memories is completely absent in the clinical assessment of patients. Aspects of neuroscience research has focused on determining how multisensory input is bound in the brain, which has been driven in recent decades by discoveries of multimodal cells in single unit recordings [24,25] and evidence that primary sensory areas are interconnected more than once realized.26 Current work has suggested that multisensory integration is critical for many complex behavioral routines to be successfully performed,27 and it should be intuitively obvious that we are always making use of multisensory input to navigate the world and this processing has to be tightly interwoven with our memories and ability to recognize patterns in the world. Understanding the neural substrates of such integration remains in the early stages of development and clinical assessment of these fundamental yet highly complex interactions must be integrated into clinical assessments.

To advance towards these objectives, we have created the Emory Multimodal Learning Task (EMLT) and Emory Pediatric Multimodal Learning Task (EPMLT), a set of novel tools specifically designed for concurrent assessment of various memory processes. This task aims to evaluate both traditional memory functions, such as face/object processing and semantic/episodic learning and memory, as well as novel, intricate learning processes involving the integration of sensory information with linguistic, semantic, and episodic elements. This comprehensive assessment takes advantage of modern technological tools to present stimuli (video-clips, images) in a multiplatform (desktop, tablet) gamified environment, which allows for virtual testing to allow for longer periods of follow-up (e.g., one week, one month, etc. rather than just 30-minute recall). The video-clips feature professional actors each in a unique setting and scene, and these were produced under the supervision of SpinVFX, inc.

Using the Unity Game Engine, we developed a stand-alone application to administer this multimodal memory assessment. Each of our tasks consists of two blocks: a learning block and delayed recall block. During the learning block participants are immersed in a gamified town environment where they can view a series of 11 videos which display actors conducting daily living activities. In each video the actors introduce novel information (faces, names, locations, objects) which can be used to assess memory across multiple modalities. The delayed recall block consists of an interactive user-interface which allows participants to respond to several questions designed to evaluate participants' capacity to integrate this information effectively and accurately identify contextual features embedded within the videos. To ensure robustness in data collection, the framework is designed to be compatible with peripheral monitoring devices such as eye-tracking devices and EEG (See Figure 1).

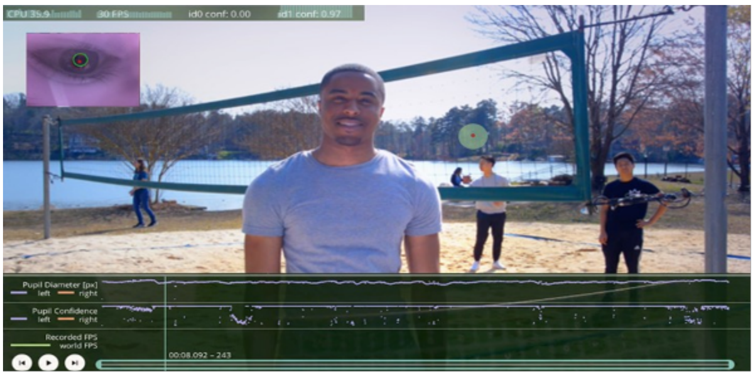

Figure 1. A new multimodal tool that is under development for the assessment of multiple domains of cognition and their integration, along with simultaneous recorded eye position and pupil diameter data.

We have successfully developed and validated this gamified framework for use in patients with epilepsy. Preliminary results indicate that this assessment can effectively measure participants' ability to successfully recall and integrate visuo-perceptual, auditory, semantic, and episodic information. Additionally, we are developing normative data for healthy subjects and patients for delayed recall intervals of 1-week and 1-month, and have found delayed recall of this more meaningful stimuli to be more recallable than traditional measures (which tend to be rote in nature). Preliminary data suggests that both memory deficits and strengths were being routinely missed by classic standard measures in our epilepsy surgery patients, and that these novel measures will allow for more thorough, ecologically valid assessments of surgical outcome, the potential for more effective rehabilitative intervention, and a heightened knowledge of structure-function brain relationships and new models of memory processes.

References

[1] Sperling, M. R., et al. (2020). Stereotactic laser ablation for mesial temporal lobe epilepsy: A prospective, multicenter, single-arm study. *Epilepsia*, 61, 1183-1189.

[2] Willie, J. T., et al. (2014). Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy (SLAH) for mesial temporal lobe epilepsy. *Neurosurgery*, 74, 569-585.

[3] Prada, F., et al. (2019). Applications of focused ultrasound in cerebrovascular disease and brain tumors. *Neurotherapeutics*, 16, 67-87.

[4] Drane, D. L. (2018). MRI-guided stereotactic laser ablation for epilepsy surgery: Promising preliminary results for cognitive outcome. *Epilepsy Research*, 142, 170-175.

[5] Drane, D. L., et al. (2015). Better object recognition and naming outcome with MRI-guided stereotactic laser amygdalohippocampotomy for temporal lobe epilepsy. *Epilepsia*, 56, 101-113.

[6] Hageboutros, K., et al. (in press). Comparison of minimally invasive to standard temporal lobectomy approaches to epilepsy surgery: Seizure relief and language outcomes. *Epilepsy and Behavior*.

[7] Gross, R. E., et al. (2018). One-year outcomes following stereotactic laser amygdalohippocampotomy for the treatment of mesial temporal lobe epilepsy: 5-year experience in 58 patients. *Annals of Neurology*, 83, 575-587.

[8] Drane, D. L., et al. (2021). Superior verbal memory outcome after stereotactic laser amygdalohippocampotomy. *Frontiers in Neurology*, 12, 779495, doi:https://doi.org/10.3389/fneur.2021.779495.

[9] Hamberger, M. J., Seidel, W. T., McKhann, G. M. n., & Goodman, R. R. (2010). Hippocampal removal affects visual but not auditory naming. *Neurology*, 74, 1488-1493.

[10] Seidenberg, M., Geary, E., & Hermann, B. (2005). Investigating temporal lobe contribution to confrontational naming using MRI quantitative volumetrics. *Journal of the International Neuropsychological Society*, 11, 358-366.

[11] Bonelli, S. B., et al. (2011). Hippocampal activation correlates with visual confrontational naming: fMRI findings in controls and patients with temporal lobe epilepsy. *Epilepsy Research*, 95, 246-254.

[12] Baxendale, S. A., van Paesschen, W., Thompson, P. J., Connely, A., Duncan, J. S., Harkness, W. F., & Shorvon, S. D. (1998). The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia*, 39, 158-166.

[13] Davies, K. G., et al. (1998). Naming decline after left anterior temporal lobectomy correlates with pathological status of resected hippocampus. *Epilepsia*, 39, 407-419.

[14] Drane, D. L., et al. (2024). Selective posterior cerebral artery Wada better predicts good memory and naming outcomes following selective stereotactic thermal ablation for medial temporal lobe epilepsy than internal carotid artery Wada. *medRxiv*.

[15] Wagner, K., et al. (2013). Memory outcome after hippocampus sparing resections in the temporal lobe. *Neurology, Neurosurgery, and Psychiatry*, 84, 630-636.

[16] Donos, C., et al. (2018). Laser ablation for mesial temporal lobe epilepsy: Surgical and cognitive outcomes with and without mesial temporal sclerosis. *Epilepsia*, 59, 1421-1432.

[17] Saling, M. M. (2009). Verbal memory in mesial temporal lobe epilepsy: Beyond material specificity. *Brain*, 132, 570-582.

[18] Basile, B. M., & Hampton, R. R. (2018). Nonnavigational spatial memory performance is unaffected by hippocampal damage in monkeys. *Hippocampus*, 1-9.

[19] Zola-Morgan, S., Squire, L. R., Amaral, D. G., & Suzuki, W. A. (1989). Lesions of the perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *Journal of Neuroscience*, 9.

[20] Drane, D. L., et al. (2008). Category-specific naming and recognition deficits in temporal lobe epilepsy. *Neuropsychologia*, 46, 1242-1255.

[21] Drane, D. L., et al. (2013). Famous face identification in temporal lobe epilepsy: Support for a multimodal integration model of semantic memory. *Cortex*, 49.

[22] Ponds, R. W. H. M., & Hendriks, M. (2006). Cognitive rehabilitation of memory problems in patients with epilepsy. *Seizure*, 15, 267-273.

[23] Corcoran, R., & Thompson, P. (1993). Epilepsy and poor memory: Who complains and what do they mean? *British Journal of Clinical Psychology*, 32, 199-208.

[24] Meredith, M. A., Nemitz, J. W., & Stein, B. E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *Journal of Neuroscience*, 7, 3215-3229.

[25] Meredith, M. A., & Stein, B. E. (1983). Interactions among converging sensory inputs in the superior colliculus. *Science*, 221, 389-391.

[26] Foxe, J. J., et al. (2000). Multisensory auditory-somatosensory interactions in early cortical processing revealed by high density electrical mapping. *Cognitive Brain Research*, 10, 77-83.

[27] Lagarde, J., & Kelso, J. A. S. (2006). Binding of movement, sound and touch: Multimodal coordination dynamics. *Experimental Brain Research*, 173, 673-688.