The Clinical Utility of Electrophysiology for Assessing and Treating Memory Impairments

Early Detection Conundrum. Physicians are uniquely charged to effectively determine the cause of patient complaints and to do so early in the course of a potential disease in order to maximize convalescence. Early recognition urgency is especially salient for the growing number of patients presenting with memory loss, where upwards of 20% of those age 65 and older already have detectable symptoms of mild cognitive impairment[22]. The medical standards for early detection were formalized by the 2011 and 2012 National Institute on Aging and Alzheimer's Association Standards[23] for Alzheimer's disease stages: *preclinical Alzheimer's disease*, *mild cognitive impairment (MCI) due to Alzheimer's disease,* and *dementia due to Alzheimer's disease*. In support, the 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for a diagnosis of mild neurocognitive disorder requires ***evidence*** of modest decline that begins to impact functional capacity, but is not yet severe enough to interfere with everyday activities.

While there is no denying the importance of early detection, physicians are hindered by a medical system that does not often afford ample time for the exhaustive interview and testing. Even if time were made available, the lengthy neuropsychological screening tests (e.g., Mini-Mental Status Exam, Blessed Dementia Scale) lack requisite sensitivity for preclinical memory disorder detection. These methods also don't lend much support to the discrimination of dementia causes from other potentially reversible conditions (e.g., depression, thyroid disorder, infection) that mimic neurodegenerative dementia. When patients present with concerns of needing greater mental effort to perform daily activities, the physician needs a very fast, very easy-to-use, low-cost, objective, and sensitive test.

Neuropsychological tests completed on the computer like ANAM, MicroCog, and CNS Vital Signs have certainly helped over the past decade and still have their place; however, these fall short in that they can take well over an hour to complete by a trained technician and, more concerning, they are largely effort based. A problem with effort based computer tests is that the degree of motivation, effort, and vigilance that the patient puts forth at the time of testing will significantly skew the resulting scores, thereby changing the interpretation. Neuropsychologists are trained to take this into consideration, but technicians and testing software cannot account for this variable. As a result, traditional and dedicated neuropsychological testing is in many respects better when administered by expert neuropsychologists. The problem with this option is that the testing will require several hours to complete, in addition to the time it takes to score, generate, and interpret a meaningful report. This is all without mention of the higher economic cost. Additionally, many neuropsychological tests are indeed objective; however, they are not direct measures of actual human physiology (e.g., Block Design). Efforts to develop blood and cerebral spinal fluid tests are active areas of research, but to date none have ample sensitivity or reliability. When searching for non-intrusive and office based options, this only leaves the objective electrophysiology measures. Electroencephalography (event related potentials, quantitative EEG analysis) in particular has a long history of strong clinical research, but, due to the expensive and sensitive equipment, has historically been out of reach from practicing doctors. EEG data collection and data interpretation is also difficult and time consuming for physicians.

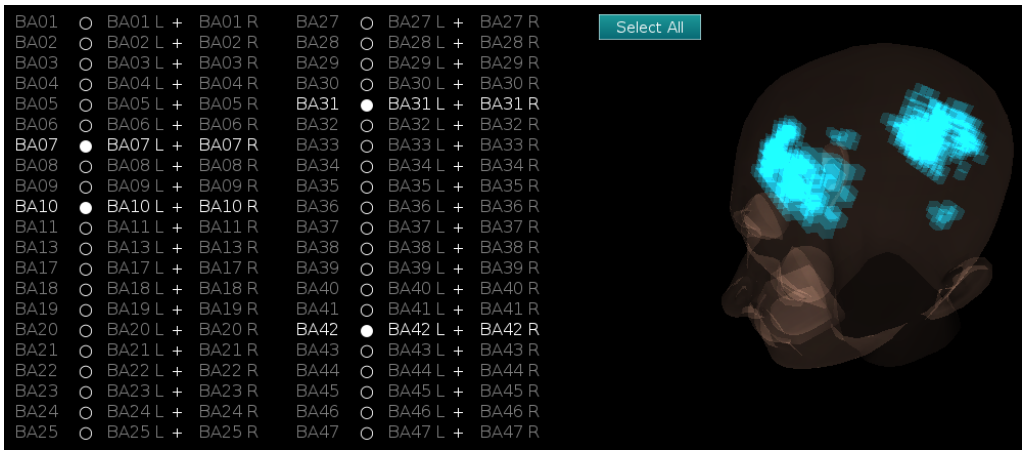
Office Based Solution. With the advent of faster computers and new advances in software, objective electrophysiology assessment and analysis are now technically available outside of brain research centers and universities. Evoke Neuroscience, Inc. is the leading medical device company providing low cost nervous system physiology measurement and biofeedback treatment equipment designed specifically to suit the needs of medical doctors and their patients. The highest standard of excellence in electrophysiology hardware and integrated software is now portable and automated so that medical assistants can skillfully offer physician-determined care to patients presenting early symptoms of cognitive dysfunction. The physician utilizes resulting graphic displays of brain images and calculated normality statistics of brain functions and heart rate variability[24-26] to help recognize early dementia conditions and offer non-invasive neurotherapy treatments predicated on the Evoke assessment.

Brain Mapping Biomarkers. Alzheimer's disease represents the most feared neurodegenerative condition accounting for the majority (60-80%) of late life dementias. However, multiple other memory and cognitive disorders (e.g., frontotemporal lobar degeneration, vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, Creutzfeldt-Jakob disease) are also considered in the initial screening evaluation of a patient in the course of determining a diagnosis and early treatment. A hallmark symptom of dementia is memory loss and, up until recently, most providers have relied on self-report questionnaires and effort-based computerized testing. The use of effort-based tests and questionnaires, when applied optimally, can identify the more severe memory impairments but often fall short in the detection of early or less severe disease presentations. Further, the memory questionnaires and effort-based screening measures do not rely on objective biomarkers that allow doctors to target specific brain regions and functional neuro networks from which the memory dysfunctions supervene. Alternatively, existing imaging studies performed outside of the primary care clinic yield some objective biomarkers but carry the disadvantage of being more invasive and costly. Nevertheless, fMRI and SPECT studies allow for a detailed look at cortical and subcortical brain structures with good spatial resolution of hippocampal atrophy for example.

Beyond brain volume loss biomarkers, the brain's capacity to allow normal productive function relies heavily on a complex array of interconnected networks that facilitate communication within and across brain structures. To understand and influence brain function, and more specifically memory, there is a need to isolate these key structures that contribute to the human ability to think and function to sustain life. Throughout the 1900s, regions of the cortex were cytoarchitecturally organized into functional locations called Brodmann Areas (BA). BAs remain a well-respected and widely referenced system for brain mapping. These cerebral divisions provide researchers and clinicians with a common descriptive tool to identify, assess, and even treat brain dysfunction. For example, a well correlated finding in early dementia is hypofunction in a portion of the dorsolateral prefrontal cortex (BA 9 and 46) associated with not just memory, but with executive functions such as organization and decision making. Other BAs have been found to correlate with frontotemporal dementia (FTD) and frontotemporal lobar degeneration (FTLD). The physician's ability to derive statistical scores on the BAs throughout the patient's brain allows not just determination of deviation from normalcy, but a system by which treatment benefits and disease course can be objectively monitored. Advancement of quantified

electroencephalography (EEG) and event related potentials (ERP) with brain source localization technologies (sLORETA) has led to a rapid expansion of the physician's ability to offer patients both non-invasive and low cost neuroimaging for memory disorders and other brain related conditions. Brief EEG/ERP recordings obtained in an awake, drowsy, and task condition, can now provide sensitive brain function measures and brain structure localization with excellent temporal resolution. The full scalp EEG data allows for several empirically validated measures that not only aid in an initial functional screening, but allow for treatment efficacy tracking over time, assessment of neuromodulation (tDCS, rTMS) effects, and implementation of neurofeedback therapy[7, 12-14] (Figure 1) with greater spatial accuracy than other interventions.

Figure 1. Evoke 4-D Brain Source: BCI targeting somatosensory motor cortex, anterior prefrontal cortex, dorsal posterior cingulate cortex, primary and auditory association cortex

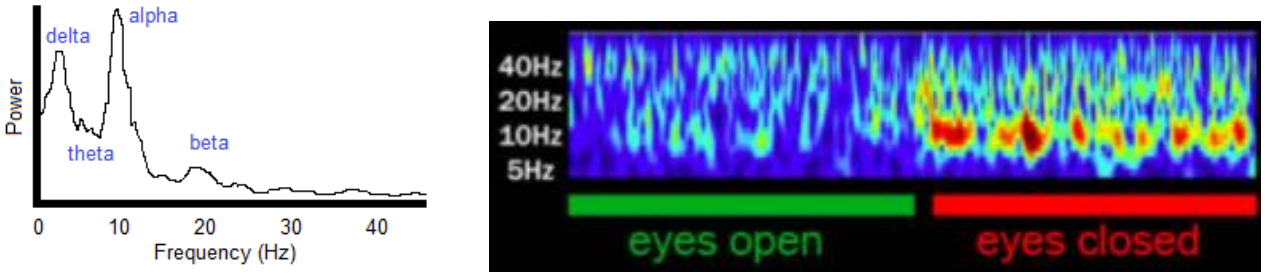


Three electrophysiology measurement categories relevant to memory function are thalamic generated alpha frequency (posterior alpha peak frequency), the P300 component of event related potentials (ERPs), and brain structure (Brodmann areas) scoring against a normal reference group. One advantage of looking at functional measures is that these appear to be more sensitive in early detection than structural MRI measures of hippocampal atrophy. A second advantage of combining these electrophysiology biomarkers is they are fast and easy to obtain with low cost equipment. A third advantage of these measures is that they can be obtained within any office setting with limited staff training or time.

Alpha Peak Frequency. The most dominant EEG frequency found in the brain is within the alpha frequency band (8 to 12 Hz) and while it has several implicated roles[3] in brain function, it is generally agreed to be a good measure of information processing[4] capacity, by which the brain is able to access the relevant and very complex storage of information. One might even describe this function as the most salient feature of memory. While the alpha frequency is generated from different locations within the brain, it is generally accepted that the thalamus generates most of the signal recorded from the parietal and occipital scalp locations. Alpha frequency is more easily identified in the eyes closed

condition (thought to be an inhibition state) due to an increase in alpha frequency amplitude. This is often graphically displayed using Fast Fourier Transform (FFT) (Figure 2).

Figure 2. FFT of 0-40Hz EEG power (left) and wavelet analysis of increased alpha amplitude during eyes closed compared to eyes open condition (right).



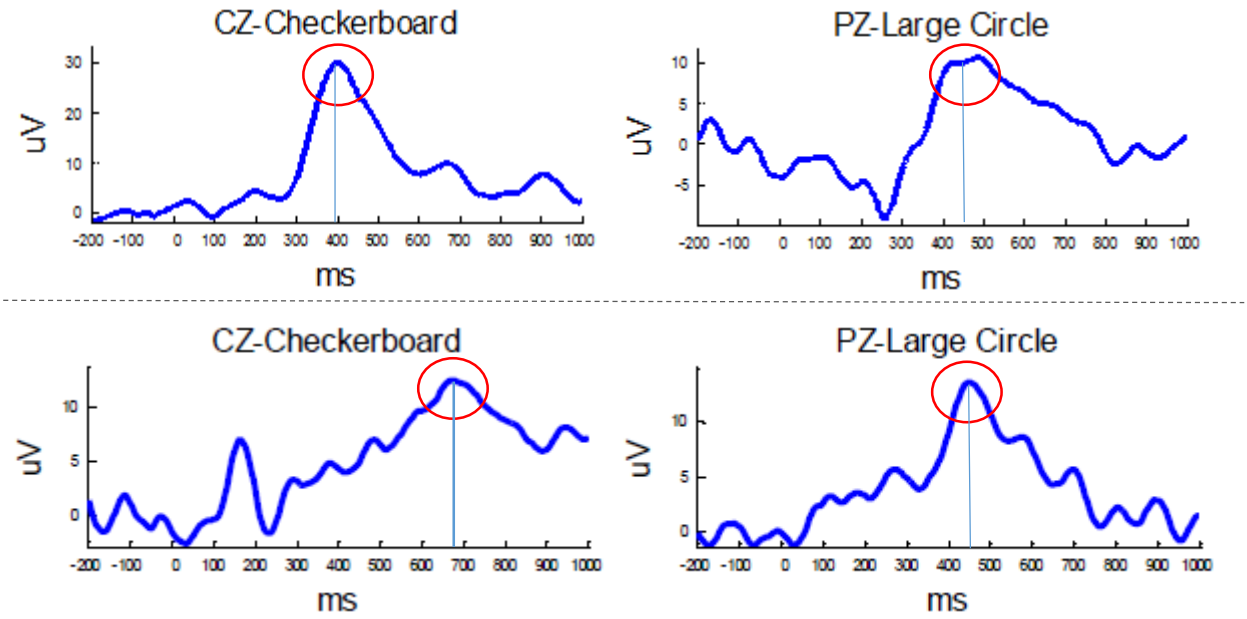
Low peak frequencies below 8Hz have been correlated with cognitive disturbances and dementia[5,6], while elevated peak alpha frequencies close to 12Hz have been correlated with good semantic memory in some normal patients. However, faster alpha peak frequencies at or over 12Hz have in some patients been correlated with central nervous system over-arousal conditions[27].

P300. Memory functions and cognitive processes within the brain can be measured using event related potentials (ERPs). The measure has been widely used to inform on condition, severity and treatment effects[8]. With the use of ERPs, one can quantify time-locked neuronal responses following presented stimuli. The time delay between stimulus onset and a patient's physical response is termed 'latency', while the recruitment and subsequent neuronal activation is represented by the component's amplitude. Longer, or delayed, latency is correlated with normal aging and also cognitive impairment[9,36]. The brain's capacity to encode information, an important element for memory storage and retrieval, is reflected in the component amplitude around 300-400 milliseconds from the target stimulus onset. Stimulus type and complexity (e.g., auditory vs. visual) will result in a variation of this latency such that a complex visual stimulus may result in a component amplitude peak near 400ms, while a simple auditory tone discrimination may be associated with a normal component amplitude peak near 350ms.

Fundamental elements of memory involve the degree of attention to a stimulus and the subsequent encoding of information for storage and retrieval. Two ERP components that have been useful to measure both these cognitive processes are known as P300a and P300b. The P300a may be used to measure frontal lobe activity related to the hippocampus, but it is also found to be a measure of the focal orienting response and vigilance to novel stimuli. Patients with significant delays in the P300a will often report memory difficulties, but the etiology may have more to do with inattention than the subsequent encoding. Those with frontal lobe dysfunction or hippocampal lesions will often show a P300a component with low amplitude and longer latency values. The P300a is mediated by dopamine and, therefore, dopaminergic binding medications result in an increased P300a amplitude and shorter latency. P300a has a maximum amplitude centrally and is therefore most often quantified at vertex

scalp location, CZ. Thus, the frontal ERP components reflect frontal working memory functions or dysfunctions. The P300b component, however, is mediated by norepinephrine[10], is generated in the medial temporal lobe, and its maximal amplitude is located in the temporal-parietal junction[11]. As a result, the P300b is most often quantified at the more parietal location, PZ. Low P300 amplitudes and longer latency measures are associated with aging and dementia conditions and indicate cortical and subcortical dysfunctions that allow the brain to inhibit unrelated information and stimuli. The combination of the both P300a and P300b encompass a part of the memory network between the frontal and temporal-parietal regions. So, these two components can be useful in differential diagnosis, neurofeedback and neuromodulation therapy, and to track treatment effects or disease course (Figure 3).

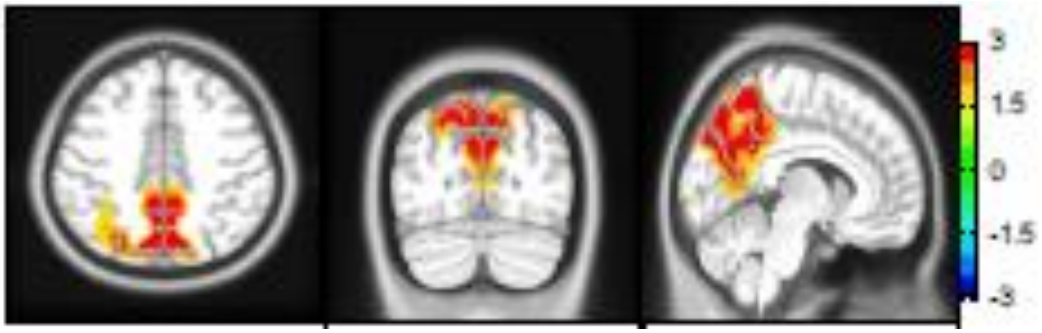
Figure 3. (Top row) P300a and P300b morphology of a 20-year-old male. (Bottom row) P300a and P300b morphology of a 45-year old male with early frontotemporal dementia reflects low P300a amplitude and elongated P300a latency. CZ-Checkerboard is P300a; PZ-Large Circle is P300b.



Brodmann areas and LORETA Imaging. Using scalp surface EEG low-resolution brain electromagnetic tomography (LORETA, sLORETA)[15] allows added insight to differential diagnosis and treatment effects[16,17] when used in parallel with imaging libraries and published imaging research[1,2]. Low alpha frequency power in the medial frontal gyrus (BA 9, 10, 46)[17] is associated with patients that have frontotemporal dementia (FTD). Those with Alzheimer's disease (AD) display excessive power in the delta and theta frequency bands in the frontal, temporal, and occipital regions. Temporal, parietal, and occipital low alpha power has been reported to correlate with low hippocampal volume and both mild cognitive impairment and AD[19]. It appears that AD presents with EEG power abnormalities more globally than FTD and the ability to source localize to specific brain structures, using Brodmann areas,

aids the clinician in cross-correlating known structures found to be hallmarks of particular diseases. Those with normal amplitude theta and alpha oscillations tend to have normal functioning working and long-term memory[20,21] making parietal neurofeedback therapy a viable consideration. For example, FTD patients appear to have greater hypofunction in the sensorimotor areas compared to mild AD (Figure 1)[18]. Pick's disease appears to often involve dysfunction in BA 8, 12, 38 while dementia with Lewy bodies is noted to be correlational with dysfunction in BA 12, 24, 28. The sensitivity of EEG and source localization with sLORETA allows for a useful assessment measure when considering memory impairment etiology, treatment interventions, and treatment response patterns. The sensitivity of these electrophysiology measures (Figure 4) is high and when used in conjunction with symptom and history information, there is greater specificity that can allow for early detection, more individualized interventions, and medical referrals.

Figure 4. sLORETA image showing (left to right) axial, coronal, and sagittal views of a parietal region of interest found to be outside normal reference group ranges.



Conclusion. There has been a clear need for objective memory-related measures that guide and inform physicians in their provision of more targeted medication and non-medication therapies (i.e., supplements, nutrition, neurofeedback, tDCS, rTMS). Ideally, a system that provides doctors electrophysiology biomarkers also offers a method by which non-invasive therapy can be delivered. In particular, the efficacy of neurofeedback treatment for memory function improvement is gaining in the international literature[28-33]. Early research demonstrating that training peak alpha aids cognitive functions in the elderly[34] and the more recent advances in fMRI neurofeedback[35] have and moved the once research field of applied medical neuroscience to a mainstream level of accepted medical practice. Patients appreciate seeing the objective evidence of their conditions, as well as tracking their physiological change longitudinally during different treatments. Physicians appreciate the office-based, low cost tool yielding sensitive measures to help patients see the value of treatment compliance, additional biomarker information to support differential diagnosis, and a more individualized neurofeedback intervention option.

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