A NOVEL ELECTROENCEPHALOGRAPHIC METHOD TO DETECT A BIOMARKER FOR MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

by

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ABSTRACT

A NOVEL ELECTROENCEPHALOGRAPHIC METHOD TO DETECT A BIOMARKER FOR MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

Jameson Douglas Beach

A novel electroencephalographic (EEG) method was developed in order to detect a biomarker in a group of individuals with mild cognitive impairment due to Alzheimer's disease (MCI-AD). Six MCI-AD patients and eight healthy controls participated in the study. A power law model was used to predict the amplitude of the flash visual evoked potential-P2 (FVEP-P2) electrophysiological responses at five different intensities of light which were delivered via a stroboscopic lamp. Though the MCI-AD group exhibited FVEP-P2 latencies that were longer than those of age-matched controls, results of the study indicate that the power law model did not adequately distinguish MCI-AD participants from controls.

INTRODUCTION

The advancement from healthy aging to Alzheimer's disease (AD) is gradual, and the onset of the disorder is absent of any significant biological or behavioral markers, making the diagnosis of AD difficult for clinicians (Barbeau et al., 2008; Moore, Tucker, Jann, Hostetler, & Coburn, 1995; Petersen, 2004). Development of a method for the detection of AD in its earliest stages may increase the effectiveness of current treatments that may slow the progression of the disease. Difficulties in detecting the early stages of AD may also be due to the lack of agreement between researchers about the terminology and definitions of the disorder (Albert et al., 2011; Petersen, 2004). Many clinical definitions of non-demented cognitive decline exist, including late-life forgetfulness (Blackford & La Rue, 1989), cognitive impairment—no dementia (Tuokko, Frerichs, & Kristjanss, 2001), cognitive disorder not otherwise specified (American Psychiatric Association, DSM IV, 1994), and amnestic mild cognitive impairment (Petersen, 2004).

In order to develop a more comprehensive, diagnostically useful definition of early AD, the National Institute on Aging and the Alzheimer's Association workgroup (Albert et al., 2011) proposed a conceptual foundation and diagnostic criteria for pre-pathological AD. The term *MCI-AD* was proposed to define a symptomatic stage between the expected cognitive decline of healthy aging and AD. It is important to note that the term *MCI-AD* is used to indicate that the symptoms associated with MCI-AD specifically represent the accumulation of AD pathology in the brain, but they are not severe enough to affect social or occupational functioning. A typical patient with MCI-AD is one who may have some difficulty in completing complex cognitive tasks, but the abilities to complete normal activities of daily living are generally preserved.

The working group (Albert et al., 2011) was assembled because of growing evidence that the diagnosis of MCI-AD represents a phase with high conversion rates to AD, demonstrating a need for clearly defined terms and diagnostic criteria. The conversion rates from pre-dementia MCI-AD to a diagnosis of AD have been demonstrated to be 10% – 15% each year, compared with 1% – 2% for control subjects (Grundman et al., 2004; Morris et al., 2001; Wolk, Signoff, & Dekosky, 2008). Approximately 80% of those diagnosed with MCI-AD will convert to AD after only 6 years (Petersen, 2004). Other authors have established conversion rates of up to 40% in only 1 year, demonstrating the value of research on this high-risk group (Flicker, Ferris, & Reisenberg, 1991).

Given the gradual onset of MCI-AD and the absence of any significant social, biological, or cognitive markers, it has proven to be a challenge to develop a sensitive and specific diagnostic tool that can reliably detect AD-related neuropathology. The current diagnostic process for MCI-AD consists of administration of a neuropsychological test battery that may require the subjective interpretations of a clinical neuropsychologist. Albert et al. (2011) suggest core diagnostic criteria to assist clinicians in the detection of MCI-AD pathology. First, there should be concern regarding a change in the patient's cognitive status, often corroborated by a family member, friend, or clinician. Second, a neuropsychological battery should reveal impaired performance in memory functioning. Although other cognitive domains may be impacted in MCI-AD, research indicates that impairment in memory, specifically episodic memory, is most common in MCI-AD patients who consequently progress to AD. Finally, Albert et al. suggest that patients whose performance falls 1.0 to 1.5 standard deviations below the age and education-appropriate mean on a cognitive test(s) might be diagnosed with MCI-AD.

There has been a significant push to discover a valid and reliable biomarker, indicating the development of AD pathology in the brain. The incorporation of a biomarker into the diagnostic framework for MCI-AD will assist in the detection of pathological changes from normal aging to MCI-AD and from MCI-AD to AD. Much of the current research into MCI-AD biomarkers has focused on imaging areas of the brain known to have high concentrations of cholinergic neurons. Cholinergic neurons are specialized cells known to synthesize the neurotransmitter acetylcholine, which is important for attention, memory, and processing sensory input (Herholz, Weisenback, & Kalkbe, 2008). The degeneration of cholinergic projections in the brain is one of the hallmark changes associated with early AD and is thought to be related to deficits in memory as well as visual functioning (Grayson, Weiler, & Sandman, 1995; Nobuhara, Halldin, Hall, Karlsson, & Farde, 2000).

Researchers have used EEG methods to help understand the cholinergic deterioration associated with AD. The flash visual evoked potential (FVEP) is a specific EEG waveform that can be elicited by a stroboscopic lamp that represents a measure of early visual processing (Odom et al., 2004). It can be reliably measured with electrodes placed over the occipital lobe. The FVEP consists of a series of positive- and negative-going waves that represent the activation of areas within the cerebral cortex. Comprising the FVEP are the flash visual evoked potential-P1 (FVEP-P1) and the FVEP-P2 waveform components. The FVEP-P1 is the first positive-going wave in the FVEP (range 70 to 90 ms poststimulus), and it is generally thought to represent the activation of the primary visual cortex, an area with very few cholinergic projections (Coburn et al., 2005; Givre, Schroeder, & Arezzo, 1994; Jeffreys & Axford, 1972; Mangun, 1995; Michael & Halliday, 1971). The FVEP-P2 is the second positive-going waveform in the FVEP (range 127 to 167 ms poststimulus in older adults) and has been widely

established as a reliable and valid measure of cholinergic functioning in the abundantly cholinergic visual association cortex located on the lateral portions of the occipital lobe as well as the posterior portions of the parietal lobe (Coburn, Parks, & Pritchard, 1993; Herholtz et al., 2008).

Given the documented early destruction of cholinergic neurons within the visual association cortex, researchers have focused on the FVEP-P2 as a potential biomarker of AD-related pathology. Researchers have discovered a particular pattern of FVEP response in those with MCI-AD and AD. Specifically, the diagnosis of AD and MCI-AD have been correlated with a selective delay in the FVEP-P2 latency (Moore et al., 1995; Swanwick et al., 1996), but there is too much overlap among the FVEP-P2 latencies of AD, MCI-AD, and mild AD to be diagnostically useful. Despite the significant promise shown by the FVEP-P2 in detecting AD pathology, a more novel approach to the administration of the strobe flash may provide greater diagnostic accuracy.

One such approach may involve the use of a psychophysical methodology. A hallmark finding in the area of psychophysics is that the relationship between a physical stimulus and the perception of that stimulus is not linear, instead following a logarithmic curve. Stevens (1962) was credited with proposing a fundamental psychophysical law that describes the relationship between subjective perceptual magnitude and a wide range of physical stimulus intensities, including those associated with electrical shock, vibration, warmth, etc.

One notable example of this phenomenon is brightness perception. The relationship between brightness—a perception—and luminance—a physical property of light—has been studied via magnitude estimation, a process by which participants assess the perceived brightness of a brief flash stimulus. As the luminance of a flash of light (stimulus) increases, the perception

of brightness also increases, but at a much slower rate. The term used to describe this non-linear relationship is *response compression*. The power law relating the psychophysical function of psychological magnitude (brightness) $\Psi(I)$ to physical brightness of the stimulus (luminance) I is as follows: $,\Psi(I)=kI^{-.5}$. where k is a constant determined by the choice of units.

Further research regarding Stevens' (1962) power law indicates similar power laws that define the relationship between a stimulus and a physiological response. As predicted, biological systems often follow power laws, creating a pattern of physical sensation which may underlie the psychophysical power function (Gisiger, 2001; Goldberger et al., 2002). Recent research into FVEP-P2 recordings has produced analogous results, with large changes in luminance associated with a gradual increase in the FVEP-P2 amplitude, similar to the response compression power law described above (Coburn et al., 2005). Coburn et al. measured the amplitude of the FVEP-P2 of 20 healthy participants at five different stimulus intensities. The pattern of electrophysiological responses was found to be nonlinear across five different brightness conditions, paralleling Stevens' psychophysical power law. The scaling relationship observed in Coburn et al. provided an example of healthy cholinergic functioning across five different flash intensity levels. A compromised cholinergic system, similar to that seen in MCI-AD, may not be able to adapt to increasing stimulus intensity levels in the same way that the brains of healthy controls may, perhaps producing a linear pattern of physiological response by the visual associational cortex.

The purpose of the present investigation was to determine if participants diagnosed with MCI-AD would produce a pattern of electrophysiological response—in response to five stimulus intensity levels—that differed from the pattern of electrophysiological response produced by normal, healthy controls. It was predicted that those with MCI-AD would produce FVEP-P2

latencies that were significantly longer than those of controls. It was also predicted that the pattern of FVEP-P2 amplitudes produced by controls would closely follow the brightness power law proposed by Stevens (1962) more than the pattern of FVEP-P2 amplitudes produced by patients diagnosed with MCI-AD, thus providing a sensitive and specific biomarker for MCI-AD pathology.

METHODS

This section describes the methodology used in this study. The major subsections include: participants, materials, apparatus, procedure, processing of the EEG data, identification of the FVEP-P2, measuring fit of the Stevens response curve, and design and analysis.

Participants

Fourteen participants were recruited from the Anchor Clinic located in downtown Pensacola. Participants were seen at the clinic for self-reported memory problems, and they completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to assess cognitive abilities. Participants were assigned to either the MCI-AD or control group based on the clinical diagnostic criteria outlined in Albert et al. (2011). Patients who scored greater than 1.5 standard deviations below the mean on subtest scores for immediate or delayed memory were diagnosed as MCI-AD and were recruited for the MCI-AD group. Six participants matching this pattern of impairment were contacted, and they consented to participate in the study. A control group of eight was comprised of participants who scored within normal limits on all subtests of the RBANS. All patients in both groups were free of dementia and seizure disorders.

Materials

The RBANS is a neurocognitive battery that assesses five cognitive domains: immediate memory, delayed memory, visuospatial/constructional, language, and attention. Experimental investigations have confirmed the clinical utility of the immediate and delayed memory sections of the RBANS for detecting AD-related neuropathology in older adults (Duff et al., 2008; Randolph, 1998). In addition, Duff et al. demonstrated an optimal balance between sensitivity and specificity when using 1.5 standard deviations below the mean to signify a performance

decrement. This finding provides credibility for the MCI-AD diagnostic criteria developed by the National Institute on Aging and the Alzheimer's Association workgroup (Albert et al., 2011) which recommend a guideline of 1 to 1.5 standard deviations below the age and education-appropriate mean on a formal neuropsychological battery.

Test-retest reliabilities for the RBANS have proven to be satisfactory, with mean intraclass correlation coefficients for the overall RBANS at .77 for healthy controls and .84 for a clinical sample (Wilks et al., 2002). In addition, discriminant and convergent validity scores of the subsections were found to be satisfactory for language, immediate memory, delayed memory, and visuospatial sections, though weaker for the attention subsection.

Apparatus

A Grass model PS33 Plus stroboscopic lamp was controlled via a stimulus computer, an instrument that also recorded and analyzed the electrophysiological data obtained from the amplifier. A Biopac Systems MP150 with a sample rate of 1,000 samples per second was used with four 16-channel amplifiers to strengthen the signal from the recording electrodes. The data were recorded and processed with Biopac AcqKnowledge 4.1 software. A speaker facing the participant played white noise to mask the sound of the strobe light flash. The data were analyzed using IBM Statistical Package for the Social Sciences version 20.

Procedure

Upon entering the laboratory space, participants were greeted and asked to complete the informed consent (Appendix B). Participants were encouraged to ask any questions or express any concerns before the study began. Participants were then seated in a comfortable chair with a neck support to reduce strain in the neck muscles. Standard silver-silver chloride electrodes were placed at O2, OZ, and O1 based on the 10-20 International System of electrode placement.

All active electrodes were referenced to electrodes that were attached to the earlobes at sites A1 and A2. Muscle activity related to eye blink was measured via an electrode pair placed above and below the right eye.

Participants were instructed to face the strobe lamp with their eyes closed and to try to keep eye blinks to a minimum. The 13.7-cm diameter xenon strobe light was situated in front of the participant's closed eyes and faced directly at the participant. Five intensities of strobe flash (1.375, 2.75, 5.5, 11, and 22 lumen s/ft2; maximum energy 1.44J) were delivered through the participants' closed eyes. The strobe stimulus was repeated 100 times at each intensity level to eliminate random measurement error and to produce a reliable FVEP recording. In order to prevent anticipatory eye blinks during recording, randomized inter-stimulus intervals (range 750ms-1.25 sec; mean 1 sec) were used between strobe flashes. All conditions were then repeated in a counterbalanced order to control for carry-over effects and to increase internal validity of the investigation's design.

Processing of the EEG Data

The FVEP-P2 represents the second positive peak and the maximum electrical amplitude in the FVEP waveform (Figure 1; Coburn et al., 2005; Odom, 2004; Wright, Williams, Drasdo, & Harding, 1985). The FVEP-P2 was measured at the recording site O2, where previous research has demonstrated that the FVEP-P2 was most reliably measured (Coburn et al., 2005).

The raw EEG signal was high-band-pass filtered at 1 Hz to alleviate the artifact of involuntary movement and galvanic skin response. A low-band-pass filter was set at 60 Hz to remove the effects of electrical activity due to muscular activity. In addition, eye movement artifact was recorded on a separate channel and removed from all active channels through an electrooculography removal signal separation technique. The electrooculography removal

process utilized an independent component analysis to separate the muscle artifact from the active channels statistically. A comb band stop digital filter was used to remove artifacts related to 60 Hz electrical signals that result from nearby electronic equipment.

Identification of the FVEP-P2

The FVEP is obtained by offline averaging of 100 recorded trials around the flash stimulus (-200ms to +500ms) for each of five strobe intensities used. Because of the large between-subjects variation observed in the average electrical potential of the EEG wave, baseline electrical potential FVEP waveforms were established. For each participant at each intensity level, the mean electrical potential of the FVEP was set to 0 microvolts in order to measure the peak positive electrical amplitude of the FVEP-P2 in the waveform. Therefore, the amplitude of the FVEP-P2 represented the deviation from the FVEP mean.

In order to identify the FVEP-P2 of each participant objectively and reliably, a semi-autonomous method of FVEP-P2 identification was employed. A meta-analysis of 11 published studies conducted by Moore et al. (1995) indicates average FVEP-P2 latencies in healthy older adults at 147 ± 20 ms poststimulus and patients diagnosed with AD at 160 ± 32 ms poststimulus. Because the FVEP-P2 represents the largest positive-going electrical peak in the FVEP, the FVEP-P2 can be automatically identified in the data by selecting the maximum electrical amplitude between 100-300ms after the flash. Once the FVEP-P2 was identified, the amplitude of the mean FVEP-P2 of MCI-AD patients was measured in millivolts for each intensity level.

Measuring Fit of the Stevens' Response Curve

To obtain the true pattern of FVEP-P2 amplitudes for each participant in the MCI-AD and control groups, each participant's FVEP-P2 amplitude was measured at each intensity level of the strobe light. Because a counterbalance test/retest method was used, the pretest and

posttest amplitudes were averaged at each intensity level, resulting in a pattern of five averaged FVEP-P2 amplitudes, each corresponding to an intensity of strobe light.

To obtain a predicted pattern of FVEP-P2 amplitudes for each participant, a response compression model consisting of a modified version of Stevens' (1962) power law was developed. The response compression model used here resembles the power curve defined by Stevens, but instead of predicting perceived brightness associated with light intensity, this model predicted the FVEP-P2 amplitudes associated with each light intensity. This response compression model was used to determine a precise pattern of predicted FVEP-P2 amplitudes that should model the functioning of a healthy brain. The function $\Psi(I) = kI^{.5}$ was used to relate predicted FVEP-P2 amplitude, $\Psi(I)$, to strobe light luminance, I. Graphically, the exponent of .5 defines the slope of the model (Stevens, 1962), whereas the constant k defines the height of the model.

Because of the high variability in the participant data, a single constant k could not be used to produce a power function for all participants. Therefore, a constant was calculated for each participant based upon his/her data. The constant k was calculated for each case by fitting the response compression model to the observed FVEP-P2 amplitudes. According to this method, the constant k was defined as the score that minimizes the square deviation around the observed amplitudes. The equation $\sum_{i=0}^{n}(y_i - \hat{y}_i)^2$ was used to determine the square deviation around the observed amplitudes. In the above equation, the squared difference between observed FVEP-P2 amplitudes (y_i) and FVEP-P2 amplitudes predicted by the response compression model ($\hat{y}_i$) would be found at each intensity level. The summation operator, ($\sum_{i=0}^{n}$) signifies that squared differences shall be summed across all five intensity levels to determine the squared deviation around the observed amplitude. The standard error of estimate, defined by the

equation $S_e = \sqrt{\frac{\sum_{i=0}^{n}(y_i - \hat{y}_i)^2}{n}}$ represents a measurement of fit of the response compression model and would serve as a dependent variable in the study. Figure 2 shows both a true observed response curve of a participant and the response compression model that was calculated to fit the data.

Design and Analysis

This section includes an explanation of the main effect and test-retest reliability tests that were used in this study.

Main Effect. The present investigation employed a natural groups independent groups design. The natural groups independent variable was clinical status. Participants identified as being MCI-AD comprised the MCI-AD group, and all others were treated as controls. The FVEP-P2 latency was used as the first dependent variable in the study. After the FVEP-P2 was identified in each experimental condition, five pretest and five posttest FVEP-P2 latency scores were recorded for each participant. The 10 latency scores were then averaged, resulting in one final latency score per participant. This final averaged latency value served as the first dependent variable in the study. A one-way between-subjects analysis of variance (ANOVA) was performed to assess the main effect of clinical status.

The standard error of estimate was used as the second dependent variable and was defined as the average deviation between the observed FVEP-P2 amplitudes and the predicted FVEP-P2 amplitudes across five strobe intensity levels. A one-way between-subjects ANOVA was used to test the main effect of clinical status.

Test-Retest Reliability. Test-retest reliability was assessed for the overall sample as well as individual intensities to determine which strobe light intensities produced the most stable

FVEP-P2s. A bivariate Pearson product moment-correlation was used to determine the correlation coefficient for the stability of the amplitude and latency of the FVEP-P2 from pretest to posttest. A Pearson product moment-correlation was also conducted on each level of strobe light intensity to determine the relative stability of the FVEP-P2 at each level.

RESULTS

Analyses of age and RBANS scores can be seen in Table 1. Scores of the MCI-AD group were significantly lower than those of controls in both immediate and delayed memory subsections of the RBANS. Age and all other subsections of the RBANS were not significantly different between groups.

A one-way ANOVA was conducted on the data to assess potential differences in FVEP-P2 latency between those designated as having MCI-AD and those who were not. Results show that despite a lack of statistically significant effect of clinical status on FVEP-P2 latency, the effect size was quite large: [$F(1, 13)=1.973$, $p=.185$, $d=.73$, $\eta^2=.14$]. As expected, the mean FVEP-P2 latency was longer in the MCI-AD group (M=193.2ms, SD=16.63) compared to the age-matched control group (M=169.44, SD=29.68).

A one-way ANOVA was also conducted on the data to compare the effect of clinical status on the standard error of estimate associated with the fit of the response compression model. Though the mean standard error of estimate was slightly higher for the MCI-AD group (M=6.56, SD=2.77) than for the control group (m= 6.23, SD=2.76), the results indicate that the presence of MCI-AD pathology did not significantly affect the standard error of estimate at the $p<.05$ level: [$F(1, 13)=.049$, $p=.829$, $d=.12$, $\eta^2=.004$].

Test-retest reliability of FVEP-P2 amplitude and latency was measured at pretest and posttest conditions (Table 2). The overall mean FVEP-P2 latencies were strongly correlated: $r(70)=.820$, $p<.001$. Mean amplitudes of FVEP-P2 were also strongly correlated, with $r(70)=.762$, $p<.001$. The high observed reliability of the FVEP-P2 demonstrates that it is a prime candidate for use as a diagnostic biomarker for MCI-AD and AD. A further breakdown of the reliabilities shows individual reliabilities at each of the strobe intensity levels. All intensities of

strobe light flash, with the exception of the lowest intensity (1.375lumen s/ft2), produced strongly reliable FVEP-P2s. The low physical lumens of the first intensity may be too dim to probe the visual system adequately, therefore causing variability in the identification and measurement of the FVEP-P2.

DISCUSSION

The purpose of the present investigation was to determine if participants diagnosed with MCI-AD would produce a pattern of electrophysiological response—in response to five stimulus intensity levels—that differed from the pattern of electrophysiological response produced by normal, healthy controls. It was predicted that those with MCI-AD would produce FVEP-P2 latencies that were significantly longer than those of controls. It was also predicted that the pattern of FVEP-P2 amplitudes produced by controls would more closely follow the brightness power law proposed by Stevens (1962) than the pattern of FVEP-P2 amplitudes produced by patients diagnosed with MCI-AD, thus providing a sensitive and specific biomarker for MCI-AD pathology.

Consistent with previous research (Swanwick et al., 1996), those diagnosed with MCI-AD did produce delayed FVEP-P2 latencies compared to age-matched controls. The large effect size associated with the effect of clinical status on latency (d=.73, η^2=.14) demonstrated that a strong relationship existed between clinical status and FVEP-P2 latency. This finding indicates that the lack of statistical significance may be due to low statistical power (sample size). Other studies that have tested the diagnostic utility of FVEP-P2 latency have indicated similar effect size findings (Coburn, Arruda, Estes, & Amoss, 2003; Moore et al., 1995; Saito et al., 2001).

Results of the investigation show that the control group did follow the response compression model more closely than did the MCI-AD group. The average deviation from the model (defined by the standard error of estimate) was slightly lower in the control group than in the MCI-AD group. Statistical analyses indicate that the effect of clinical status on the standard error of estimate was not significant, meaning that the pattern of FVEP-P2s for healthy participants did not follow Stevens' (1962) response compression model more closely than did

MCI-AD patients. This method, therefore, did not improve upon previous methods that have examined the diagnostic utility of the FVEP-P2.

Analyses of test-retest reliabilities of FVEP-P2 amplitude and latency at each strobe intensity level, with the exception of the lowest (1.375 lumen s/ft2) intensity, indicated very high reliability coefficients. Pearson product-moment correlation coefficients were averaged across intensity to determine the overall test-retest reliability of the FVEP-P2 amplitude and latency measures. The average correlation coefficient was r=.762 and r=.820 for amplitude and latency, respectively. The lowest strobe intensity used elicited FVEP-P2 amplitude and latency coefficients of r=.657 and r=.526, respectively. Beyond the first intensity, reliability of FVEP-P2 amplitude increased with every increase in strobe intensity, increasing from r=.747 at the second intensity to r=.889 at the fifth intensity. Reliability of FVEP-P2 latency was not dependent on strobe intensity, with the highest correlation coefficient observed at the second intensity (2.75 lumen s/ft2) r=.970.

Coburn et al. (2005) demonstrated similar test-retest reliabilities for amplitude and latency at the O2 recording site using the same strobe intensities used here. The average test-retest reliabilities across strobe intensity for amplitude and latency at the O2 site were both r=.87. Coburn et al. did, however, find more adequate reliabilities for amplitude and latency (r=.90 and .84, respectively) at the lowest strobe intensity.

Limitations of the Investigation and Future Research Directions

There were several limitations that may have obscured the results of the study and led to the failure to reject the null hypotheses. The most obvious limitation of this study was low sample size. The sample size of this study (N=14), especially in the MCI-AD group (n=6), may not have been large enough to provide adequate statistical power to reject the null hypotheses

correctly. Given the large effect size of the latency findings, a Type II error may have accounted for the non-significant results of the study. Recruitment of participants was restricted to a relatively small neuropsychology clinic. Because of the very specific diagnostic criteria used to be considered MCI-AD, very few patients' test scores fit this specific pattern of cognitive impairment. Future studies would require broadening the recruitment strategy to multiple clinics and/or hospitals to obtain an adequate sample of MCI-AD patients.

Another limitation of this study was the disproportion of men and women in each group. Males predominated in the MCI-AD group (composed of 83% men), and females predominated in the control group (composed of 63% females). Thus, the sex imbalance may have affected the findings. Recruitment of a larger sample would have allowed for the balance of sex in each group to regress to an appropriate distribution.

A simple explanation for the failure to reject the null hypothesis may be that the amplitude was not the most appropriate feature of the FVEP-P2 to detect AD pathology in the MCI-AD sample. As evidenced by this study, FVEP-P2 latency may be a more suitable feature of the FVEP-P2 for use as a biomarker. Future researchers should continue to examine novel methods of strobe lamp presentation and FVEP-P2 analysis to detect a sensitive and specific biomarker of MCI-AD.

Another limitation of the study resulted from difficulties in identification of the FVEP-P2. The semi-automated mechanism for identification of the FVEP-P2 was designed to lessen the effect of experimenter bias in detection of the FVEP-P2 but may have been a source of increased variability in the data. The algorithm defined the FVEP-P2 as the highest observed amplitude in the FVEP waveform between 100 and 300 ms postflash stimulus. Random variability in the data may have produced positive-going electrical potentials in the FVEP that

surpassed the true FVEP-P2 and were incorrectly selected as the FVEP-P2, therefore giving false amplitude and latency data. Future researchers may benefit from using the semi-automated FVEP-P2 identification algorithm as a guideline as well as using expert clinicians or certified EEG technicians who can make selections based on patterns and context cues.

Conclusions

The purpose of the present study was to investigate the use of a novel method of FVEP-P2 analysis that may aid in the detection of a biomarker for MCI-AD pathology. Though the MCI-AD group exhibited FVEP-P2 latencies that were longer than those of age-matched controls, a novel method of analysis that utilized FVEP-P2 amplitudes was not significant and therefore did not result in an improved method of MCI-AD pathology detection. The findings of this study are particularly important because they further indicate the nature of the electrophysiological manifestation of MCI-AD pathology. The test-retest reliabilities of the FVEP-P2 amplitudes and latencies reported here also contribute to the knowledge base of the FVEP research. Future researchers should continue to examine the FVEP amplitudes and latencies to identify how MCI-AD pathology affects the patterns of response.

Table 1

Participant Demographics

Age and RBANS Scores of Participants

	Total (n=14, 8 men)		MCI-AD (n=6, 5 men)		Control (n=8, 3 men)			
	Mean	SD	Mean	SD	Mean	SD	F	p
Age	70.54	10.24	73.00	13.75	67.71	5.65	1.171	.302
RBANS								
Immediate Memory	88.29	19.51	72.00	14.34	100.50	12.73	15.56	.002*
Delayed Memory	85.57	22.02	62.83	11.00	102.63	6.21	74.48	.000**
Visuospatial	98.29	11.22	94.00	5.55	101.50	13.58	1.60	.230
Attention	99.29	13.79	98.50	15.38	99.88	13.53	0.03	.862
Language	97.50	8.16	97.16	10.03	97.75	7.19	0.02	.901

*p<.05

**p<.001

Table 2

Test-Retest Reliability of FVEP-P2s

Pearson product moment correlation coefficients (r)

Strobe Light Intensity	Amplitude	Latency
Intensity 1 1.375 lumen s/ft2	.657*	.526
Intensity 2 2.75 lumen s/ft2	.747**	.970**
Intensity 3 5.5 lumen s/ft2	.808**	.949**
Intensity 4 11 lumen s/ft2	.870**	.814**
Intensity 5 22 lumen s/ft2	.889**	.874**
Overall	.762**	.820**

*p<.05

**p<.001

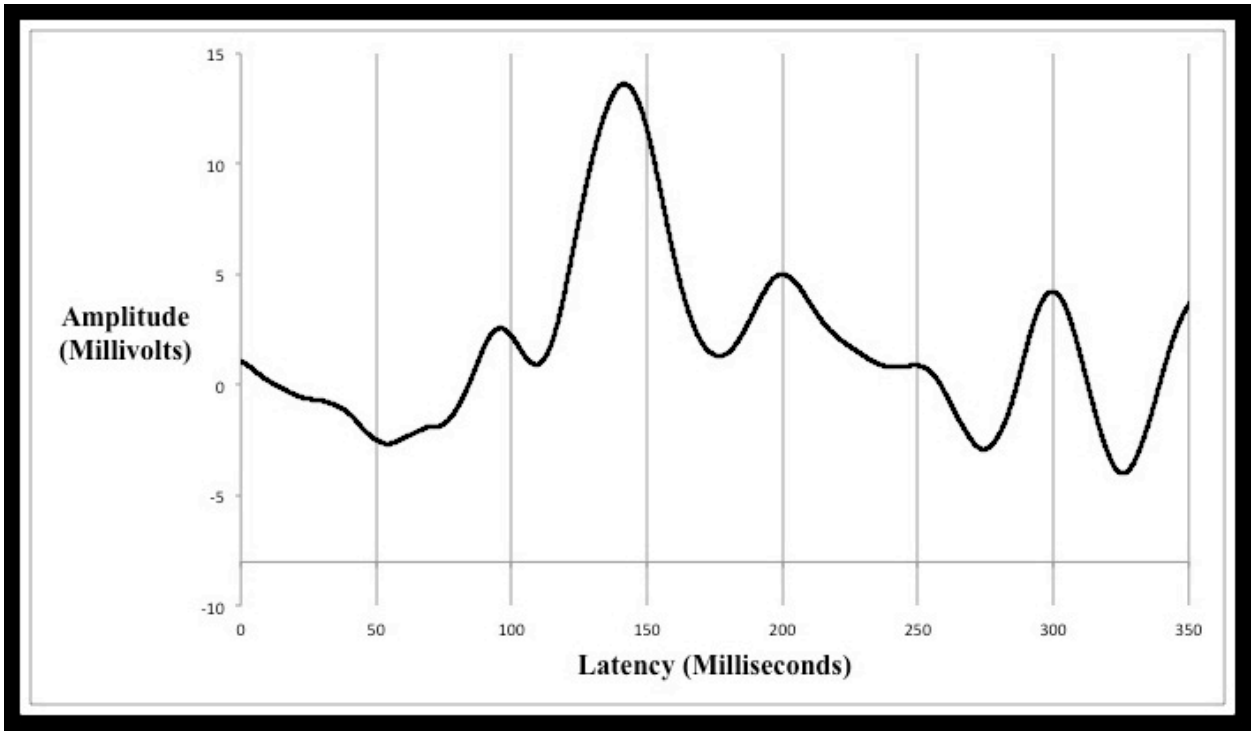

Figure 1. An example of an FVEP of a healthy control. This example represents the response to a strobe flash of 11lumen s/ft2. The flash stimulus occurs at 0ms. Note that the FVEP-P2, the highest peak in the FVEP, has an amplitude of 13.61mV a latency of 141ms.

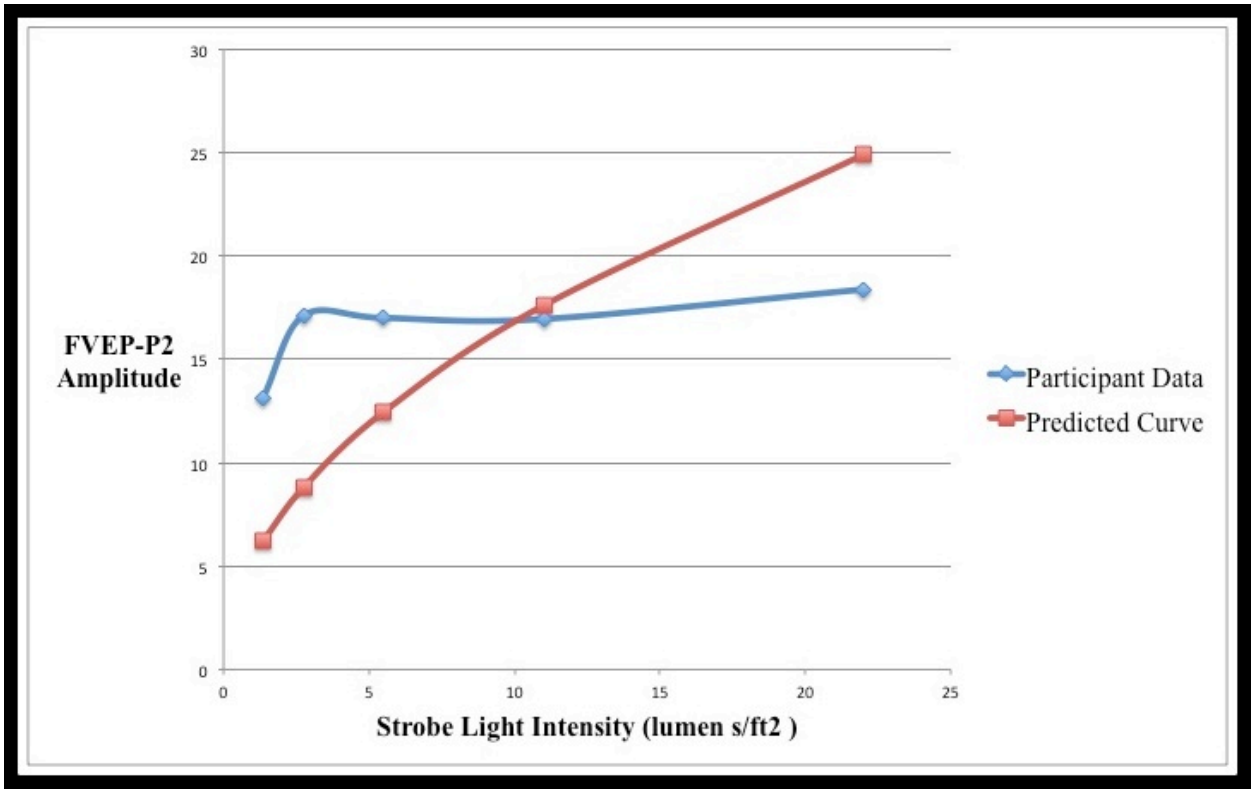

Figure 2- A calculated Stevens' response curve plotted against observed participant data. Note that both flash visual evoked potential P2 (FVEP-P2) lines share the same x-axis points, which correspond to the five intensities of strobe flash used. The standard error of estimate for the above data is 6.01.

APPENDICES

Appendix A. IRB Approval

University of West Florida

Research and Sponsored Programs
11000 University Parkway, Bldg. 11
Pensacola, FL 32514-5750

MEMORANDUM

March 11, 2009

TO: Dr. Frank Andrasik
Psychology Department

FROM: Dr. Terry Prewitt, Chair, IRB for Human Research Participant Protection

Dr. Richard S. Podemski, Associate Vice President for Research
and Dean of Graduate Studies

SUBJECT: IRB Approval

The Institutional Review Board for Human Research Participants Protection has completed its review of your proposal titled "Neuropsychological/physiological Early Detection of MCI-a" as it relates to the protection of human participants used in research, and has granted approval for you to proceed with your study. As a research investigator, please be aware of the following:

- You acknowledge and accept your responsibility for protecting the rights and welfare of human research participants and for complying with all parts of 45 CFR Part 46, the UWF IRB Policy and Procedures, and the decisions of the IRB. You may view these documents on the Office of Research and Sponsored Programs web page at http://www.research.uwf.edu. You acknowledge completion of the IRB ethical training requirements for researchers as attested in the IRB application.

- You will ensure that legally effective informed consent is obtained and documented. If written consent is required, the consent form must be signed by the subject or the subject's legally authorized representative. A copy is to be given to the person signing the form and a copy kept for your file.

- You will promptly report any proposed changes in previously approved human subject research activities to the Office of Research and Sponsored Programs. The proposed changes will not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

- **You are responsible for reporting progress of approved research to the Office of Research and Sponsored Programs at the end of the project data gathering period of March 10, 2009 to March 09, 2010.**

- You will immediately report to the IRB any injuries or other unanticipated problems involving risks to human subjects.

Good luck in your research endeavors. If you have any questions or need assistance, please contact the Office of Research and Sponsored Programs at extension 6378.

CC: Dr. James E. Arruda
Dr. Laura Koppes
Memory Disorders Clinic/WFH

Phone 850.474.2824 Fax 850.474.2802
Web research.uwf.edu

Appendix B. Informed Consent Statement

Informed Consent Statement

Title of Research: *Neuropsychological/physiological Early Detection of MCI-a*

I. Federal and university regulations require informed consent for participation in research involving human participants. After reading the statements in sections II through IV below, please indicate your consent by signing and dating this form.

II. **Statement of Procedure:** Thank you for your interest in this research project being conducted by Drs. Frank Andrasik and James Arruda, Department of Psychology, University of West Florida, and Dr. Kevin Groom, Anchor Clinic, Pensacola. By this time, one of the researchers or staff members should have described the procedures for you in detail. This research is designed to learn more about early problems with memory and how these may relate to more significant problems later in life. You will find a summary of the major aspects of the study being described below, including the risks and benefits of participating. Carefully read the information and should you wish to participate in this study, please sign and date this form. Note, you will also need to complete a second form (HIPAA) authorizing the release of some of your personal information so that we can complete our key analyses. All information provided/obtained will be kept in strict confidence and coded so that you cannot be personally identified. If you have questions regarding this project, please contact Dr. Frank Andrasik, Distinguished University Professor, UWF, at (850) 474-3298 or by email at fandrasik@uwf.edu or Dr. James Arruda, Associate Professor, UWF, at (850) 474-2361 or by email at jarruda@uwf.edu.

I understand that:

1) I will be asked to participate in a novel assessment of my brain wave activity, called the flash visual evoked potential. For this, various sensors will be placed around my head. I will then be asked to rest with my eyes closed while my brain wave activity is recorded in response to the repeated strobe (light) flashes.
2) I should not participate if I have been diagnosed with a seizure or epileptic disorder.
3) I will receive payment in the form of a $30.00 Walmart gift card when the assessments are completed.
4) The results of my participation will be confidential and will not be released in an individually identifiable form without my prior consent, unless otherwise required by law.
5) Financial compensation for such things as disability or discomfort due to injury or lost wages, etc. is not available. Any medical expenses due to self-inflicted injury are my responsibility. Unless found to be liable in a court of law for medical damages, no other

compensation for other damages is available from the University of West Florida, the Memory Disorders Clinic, West Florida Hospital, or the study investigators.

6) I may discontinue my participation in this study at any time without penalty.
7) I will be asked to sign a second form authorizing release of certain medical information to Drs. Andrasik and Arruda.
8) The Johnnie B. Byrd, Sr. Alzheimer's Center and Research Institute, Tampa, FL is funding this project, and the Researchers are required to submit findings of the project to them. Findings will be reported only in aggregate, not as individual data, and without any identifying information.

III. **Potential Risks of the Study:**

1) The only discomfort that may be faced during the flash visual evoked potential is boredom, fatigue, and/or itchiness of the scalp.

IV. **Potential Benefits of the Study:**

1) I will receive a gift card to help offset some of my costs associated with participating.
2) Information obtained from this study may provide a better understanding of the nature of memory problems, which may in turn lead to insights in treating and/or delaying the onset of more significant problems later in life.

V. **Statement of Consent:** I certify that I have read and fully understand the Statement of Procedure and agree to participate in the research study described above. My permission is given voluntarily without coercion or undue influence. I understand that I may discontinue my participation at any time without penalty or loss of any benefits that I may be entitled. I also understand that I can have the results of my participation, to the extent that it can be identified as mine, returned to me, removed from the research records, or destroyed. I will be provided a copy of this consent form. Any questions I have are written below and have been discussed with the experimenter.

_____

_____

Participant Questions (if any)

_____ _____

Participant's Name (Please Print) Date of Birth

_____ _____

Participant's Signature Date

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