# Complementary EEG Evidence for a Significantly Improved Alzheimer's Disease Case after Photobiomodulation Treatment

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## INTRODUCTION

- Photobiomodulation (PBM) therapy is a safe, non-invasive modality based on research dating back to the 1960's.
- PBM or low-level laser (or light) therapy (LLLT) uses either visible red or near-infrared (NIR) light to stimulate, heal, and repair damaged or dying cells and tissues.
- Mechanisms of action involve the stimulation of the mitochondria, leading to biochemical activities that result in brain cell recovery.
- PBM is applicable to a diverse range of brain conditions through the use of transcranial PBM (tPBM).
- A recent case series report presented for the first time, significant improvement in dementia patients after transcranial plus intranasal PBM treatments with NIR light at the wavelength of 810 nm.[1] The phenomenon calls for evidence to verify that the brains were responding to PBM and not to other external stimuli.
- This is a follow-up study introducing electroencephalography (EEG) to investigate the case of a newly recruited Alzheimer's disease (AD) patient. The objective was to observe whether there were significant EEG changes to support changes in cognition. Real-time EEG response would help to verify that the brain responds to tPBM.
- Certain modifications were made to the protocols of the earlier study by incorporating parameters that were hypothesized to improve outcomes: 1) The pulse rate was changed from 10 Hz (alpha) to 40 Hz (gamma). 2) Patients were given the headset to use at home for once a night, 6 nights a week. 3) Fewer light emitting diodes (LEDs) were used, but more precisely targeted at the hubs of the default mode network (DMN), with more power.

## METHODS

### Device and Protocol

The study used 810 nm, 40 Hz pulsed, light-emitting diode (LED) devices combining transcranial plus intranasal PBM from Vielight Inc. called the Vielight Neuro Gamma, to treat the cortical hubs of the default mode network (DMN). Each treatment is auto-timed for 20 minutes. The patient had a baseline Mini-Mental State Examination (MMSE) score of 21. He received the PBM intervention at home or in a long-term care facility for 1x/day, 6 days/week for the 17 weeks covered in this study. The protocol was administered by caregivers.

### Cognitive Daily Living Scales

The patient was administered the MMSE and the Alzheimer's Disease Assessment Scale - cognitive (ADAS-cog) at Weeks 0, 3, 7, 12 and 17 and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) at Weeks 0 and 3.

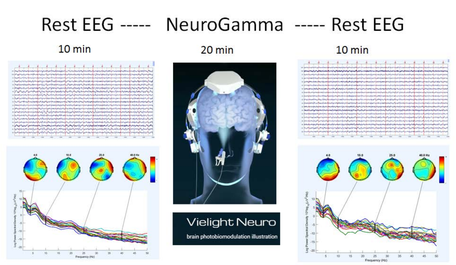
### Data Collection of Variables for Normal Functioning

A daily log covering 21 days was maintained by the subject's caregiver covering 13 variables related to cognition expected for a reasonable quality of life. The variables covered eye contact, demeanor, writing motor skill, other motor skills, reading, email usage, orientation, long term memory, short term memory, clarity of expression, critical and abstract thinking, conversation and mood. They were rated on an ordinal category scale of 0 to 10.

### EEG Data Collection

EEG data were collected using a 19-channel Free-cap system (Institut für EEG-Neurofeedback, München, Germany) and BrainMaster Discovery 20 (Brainmaster Technology Inc., Ohio). In this EEG system Ag/AgCl electrodes contact sponges were saline-soaked and positioned tightly on the scalp to ensure proper contact. The impedance of all electrodes was lowered to ≤5 kΩ. EEG signals were recorded using DC and a low-pass filter anti-aliasing filter, of 0-60 Hz, at 256Hz sampling rate. All electrodes were referenced to the linked mastoid electrodes. EEG data were collected during a 10-minute rest period with eyes closed before transcranial near-infrared stimulation (tNIRS), and then for 20 minutes after tNIRS, as presented in Figure 1.

**Figure 1: Study Design for EEG Data Collection**




### EEG data preprocessing

EEG data were processed offline using a custom MATLAB script (MathWorks, MA, USA), and EEGLAB toolbox (Swartz Center for Computational Neuroscience, University of California at San Diego). First, EEG data were visually inspected to remove highly contaminated artifacts. Thereafter, EEG data were digitally filtered by using second order, Butterworth, zero-phase shift 1-55 Hz band pass filter (24dB/Oct), and segmented into 2 sec epochs. Then, an electrodes-by-trials matrix of ones was created and assigned a value of zero if an epoch had: (1) amplitude larger than +/- 150 µV; (2) power spectrums that violated 1/f power law; or (3) standard deviation 3 times larger than the average of all trials. Fourth, an electrode was rejected if its corresponding row had more than 60% of columns (trials) coded as zeros. Fifth, an epoch was removed if its corresponding column had more than 20% of rows (electrodes) coded as zeros. Sixth, an independent component analysis (ICA) (EEGLAB toolbox; Infomax algorithm) was performed to remove ocular, muscle artifacts, and other noise from the EEG data. Finally, data was re-referenced to the average for further analysis.

### EEG power spectrum analysis

Power spectrum analysis was performed using Morlet wavelet decomposition, as implemented in EEGLAB newtimef() function. The decomposition produced a linear frequency space with 100 frequencies ranging from 1 to 50 Hz, and a time space with 200 time points ranging from -1000 to 1000 ms. To account for the trade-off between frequency and temporal resolution, the wavelets were modified, such that wavelet cycles increased linearly form 0.5 to 10 cycle for the lowest frequency (1 Hz) to the highest frequency (50Hz). Finally, the mean log power was calculated for each frequency: Delta (1-3) Hz, Theta (4-7) Hz, Alpha (8-14) Hz, Beta (14-30) Hz and Gamma (30-50) Hz.

## RESULTS

### RAPID IMPROVEMENT IN NORMAL FUNCTIONING

Based on the ordinal categorical scores of cognition-related variables for normal functioning, significant changes were already observed from the second day of treatment, such as improvement in eye contact from 1/10 to 9.2/10. By the second day, the patient was emerging from silence and starting to hold meaningful conversations, and able to write. By the third week, he has regained most of his quality of life, with much improved ability to communicate. These are shown in Table 1.

**Table 1: Changes in Selected Ordinal Categorical Normal Functioning Variables**

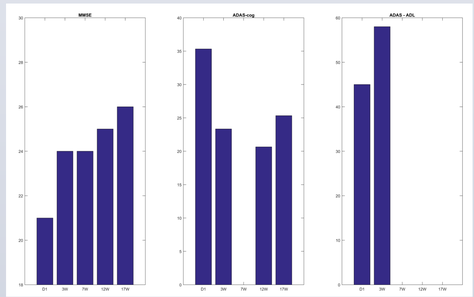
| | Treatment | | | | | |
|---|---|---|---|---|---|---|
| Variable | Day 0 | 1 | 2 | 7 | 14 | 21 |
| Eye contact | 1 | 1 | 9.2 | 9.8 | 9.8 | 9.8 |
| Demeanor | 1 | 1 | 3 | 5 | 7 | 8 |
| Motor skill - writing | 0 | 0 | 4 | 7 | 7 | |
| Motor skill - other | 0 | 0 | 4 | 7 | 7 | 8 |
| Reading | 0 | 0 | 0 | 5 | 6 | 8 |
| Email | 0 | 0 | 0 | 4 | 7 | 8 |
| Orientation | 1 | 1 | 0 | 4 | 5 | 8 |
| Long term memory | 4 | 4 | 4 | 5 | 6 | 8 |
| Short term memory | 2 | 2 | 4 | 4 | 5 | 6 |
| Clarity | 4 | 4 | 5 | 6.5 | 6 | 6 |
| Critical and abstract thinking | 1 | 1 | 3 | 6 | 8 | 8 |
| Conversation | 1 | 1 | 4 | 6 | 6 | 7 |
| Mood | 1 | 1 | 3 | 4 | 7 | 8 |

Note to Table 1: Scales are expressed from 0 to 10.

### COGNITIVE AND DAILY LIVING IMPROVEMENTS OVER 17 WEEKS

Based on MMSE and ADAS-cog scales, the greatest rate of improvements were experienced in the first 3 weeks. For this report, we managed to collect data over a total of 17 weeks. As presented in Figure 2, MMSE increased from 21 at baseline to 26 at Week 17 and ADAS-cog improved from 35 to 25. We covered 3 weeks for the ADCS-ADL scores, which showed improvements from 43 to 58.

**Figure 2: MMSE, ADAS-cog over 17 weeks and ADCS-ADL over 3 weeks**




### IMPROVEMENT IN BASELINE EEG POWER

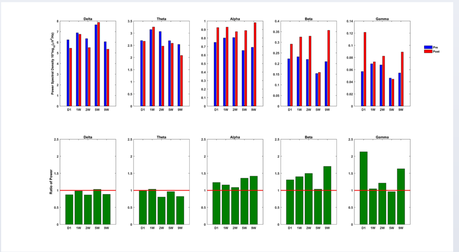
These cognitive improvements were accompanied by baseline oscillation changes in the delta, theta and alpha frequency bands expressed in EEG readings. Over 3 weeks, the absolute power of alpha frequency increased significantly from 5.1 µV2 to 12.7 µV2, and the peak of the alpha wave oscillation shifted from 8.6 Hz into 9.3 Hz. In addition, the absolute power of delta and theta increased from 1.86 µV2 to 2.9 µV2 and 2.12 µV2 to 3.7 µV2, respectively.

### ACUTE SHORT-TERM POWER ELEVATION OF GAMMA, BETA, ALPHA, AND REDUCTION OF THETA, DELTA

The above global increase in EEG power was observed over a duration of 3 weeks. Measured during each of the few minutes of treatment, we observed significant and consistent acute changes/entrainment during each 20-minute treatment.

During each tPBM treatment, significant elevation in the higher frequency oscillations in gamma, beta and alpha were observed. On the other hand, the theta and delta oscillations were reduced. These are illustrated in Figure 3.

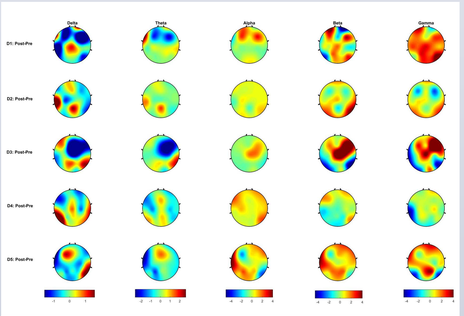
**Figure 3: Acute Short-term Changes in Brain Oscillations**




Note to Figure 3: We utilized a sham device in the Week 5 measurement, and there was no change in the gamma and beta power spectral density, which supports the theory that the brain responds to an active (but not to sham) Neuro Gamma device. There were also no significant changes in the theta and delta oscillations. The change in alpha oscillations were expressed because the subject closed his eyes during the sessions.

When presented as qEEG brain maps, we observe consistent patterns in elevated gamma and beta power and reduced theta and delta power. This is shown in Figure 4.

**Figure 4: qEEG Brain maps Representing Acute Short-term Entrainment**




Note to Figure 4: Generally blue indicates lower power, and red higher power in comparison to a normative data base. The intensity of the colors reflects the magnitude of the standard deviation as represented by z-scores.

## CONCLUSION

In this case report, delivery of near infrared light at 810 nm to the hubs of the default mode network, pulsed at 40 Hz produced significant improvements in:

- cognition (measured over 17 weeks)
- daily living and quality of life factors (measured over 3 weeks)
- electrophysiological baseline power over 3 weeks, across all oscillations
- acute short term entrainment after each treatment, elevating gamma, beta and alpha oscillations; and attenuating theta and delta oscillations.

Outcomes were rapid and significant, noticeable within days, continuous and sustained over 3 weeks. The metrics continued to improve over the 17 weeks of the study. No negative side effects were observed.

## DISCUSSION

Mitochondrial activity has been increasingly accepted as the underlying foundation for photobiomodulation (PBM) mechanism.[2] The EEG data in this report provides a physiological explanation to help fill the gap between that basic mechanism and human medical outcomes. They also provide new validation to tPBM as a modality that can modulate brain functions.

The significant improvement in outcomes related to AD in this report could partially be contributed by the 40 Hz pulse, activating microglia to reduce the burdens of β-amyloid and tau proteins.[4] This parameter is a modification of the pulse rate of 10 Hz used in the previous case series report[1].

The baseline improvement in absolute power of brain oscillations over time supports the cognitive improvements as measured with the MMSE and ADAS-cog scales, as well as daily living factors measured in ADCS-ADL and ordinal categorical data of selected variables. They reflect improved DMN function[3], supporting the potential of transcranial plus intranasal PBM as a safe and effective treatment for AD.

The modulation of the different brain oscillations provides new insights into how PBM has increased cognitive processing capacity. This capability is expressed as enhanced power in the gamma and beta ranges. Elevated delta and theta have been associated with reduced cognitive processing, so the reduction in the power of these oscillations further supports improved cognition.

This study involved a sample of 1 but provided compelling data to move forward to more investigations with PBM for AD. It calls for studies with larger samples as well as a deeper understanding of how PBM with these parameters can modulate brain oscillation patterns.

## SELECTED REFERENCES

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