Photobiomodulation, Photomedicine, and Laser Surgery
Volume XX, Number XX, 2022

Pp. 1–6
DOI: 10.1089/photob.2021.0048

Case Report

Reversal of Acquired Prosopagnosia Using Quantitative Electroencephalography-Guided Laser Therapy

Robert Hedaya, MD[1,i] and Joel Lubar, PhD[2]

Abstract

Background: Currently treatment for prosopagnosia is limited.
Methods: We report the reversal of acquired associative-type prosopagnosia (AAP) using quantitative electroencephalography (qEEG)-guided transcranial laser therapy (qGLT) in a subject with temporal lobe epilepsy (TLE) and mild cognitive impairment (MCI).
Results: Objective and subjective measures of improvement in AAP, TLE, and MCI are presented. Additional improvement, measured through qEEG, was found 1-month post-treatment.
Conclusions: There was no recurrence of AAP for 1 year. We conclude that further research into the utility of qGLT in the treatment of AAP is warranted.

Keywords: prosopagnosia, seizures, qEEG, Alzheimer's, MCI, photobiomodulation

Introduction

Prosopagnosia may have a debilitating effect on socio-economic and emotional function.[1–3] It may follow a lesion, stroke, head trauma, or no discernible cause. There are no medical or surgical interventions for acquired associative-type prosopagnosia (AAP). Attempts to remediate AAP[3,4] have met with limited success.[5,6]

Photobiomodulation (PBM) of the brain is being explored for a variety of neurological disorders including dementia,[7–10] Parkinson's disease,[11] stroke,[12] traumatic brain injury,[13–17] depression,[18] and post-traumatic stress disorder.[16,19] A primary mechanism of PBM is dissociation of nitric oxide from mitochondrial cytochrome c oxidase, allowing increased adenosine triphosphate (ATP) production, and increased local blood flow.[20,21] Since there have not been any published reports of PBM for prosopagnosia, alleviation of prosopagnosia was not expected.

We reasoned that since an energy deficit is a significant aspect of neuronal dysfunction and Alzheimer's disease (AD),[22] increasing ATP could be helpful in supporting disturbed neuronal functions in an apolipoprotein epsilon (APOE) homozygote with AAP, temporal lobe epilepsy (TLE), and mild cognitive impairment (MCI). Further we reasoned that determining the cortical locations to target through quantitative electroencephalography (qEEG)-symptom matching would increase the likelihood of meaningful clinical benefit. Finally, monitoring patient response and tissue response (through qEEG) would give us a basis for adjusting treatment parameters. In toto, this method could provide therapeutic gain. We used high-intensity laser due to depth of tissue penetration,[23] efficiency, and the ability to treat specific regions with specific parameters.[24]

We report the unexpected reversal of AAP, co-occurring TLE, and MCI through quantitative-guided transcranial laser therapy (qGLT) with further progressive improvement of qEEG 1-month post-treatment.

Clinical history

A 58-year-old postmenopausal APOE-4 homozygote presented (May 2018) with a 7-year history of prosopagnosia, impairment of episodic memory, word retrieval, forgetfulness, and untreated TLE. Toxic exposures included a 30-year history of alcohol use, 28 pack-years of smoking, and a 6-month occupational exposure to reduced oxygen, elevated CO_2, nitrous oxide, and mercury.

Family history

Family history revealed five APOE-4 first degree relatives and two aunts with dementia.

[1]The Whole Psychiatry & Brain Recovery Center, Institute for Functional Medicine, Georgetown University School of Medicine, Rockville, Maryland, and Washington, DC, USA.
[2]Southeastern Neurofeedback Institute, Inc., Professor Emeritus University of Tennessee, Pompano Beach, Florida, USA.
[i]ORCID ID (https://orcid.org/0000-0002-2251-8893).

Timeline

Age 4: TBI-unconscious for several hours
Age 24–51: 3–4 alcoholic drinks per night
Age 46: Depression
Age 50: Menopause
Age 51: Prosopagnosia onset, impaired memory, and word recall. Discontinuation of alcohol
Age 54: Accelerated cognitive decline; neurological consultation
Treated mild sleep apnea

Examination

Mild dysdiadochokinesia, vitiligo, oral thrush, moderate periorbital edema, dry skin, and a body mass index of 21 kg/m^2 were noted. MOCA score was 27/30. Mental status examination was otherwise normal.

Laboratory data

Thyroid stimulating hormone (TSH): 3.34 (0.45–4.50), free unbound thyroxine (free T4): 1.19 (0.82–1.77), and free tri-iodothyroxine (free T3): 2.8 (2.0–4.4). Thyroid function was assessed and treated in relation to its possible effect on cognitive function[25] in MCI. Melatonin: 5 (10–85); vitamin D: 34 (30–100); multiple nutritional deficiencies were identified and corrected.

Magnetic resonance imaging

Volumetric magnetic resonance imaging (MRI) revealed asymmetry of temporal lobes (70.39 left vs. 60.33 right), amygdala (54.54 left vs. 62.33 right), and cerebellum (42.17 left vs. 48.47 right). Hippocampi were symmetrical and normal in size, while total white matter was normal.

qEEG methodology

Baseline qEEG was obtained 6 months after lifestyle, nutritional, estradiol, progesterone, and thyroid interventions were in place. Three qEEGs, eyes open (EO) and eyes closed (EC) are reported: baseline: (1/04/19), after 21 treatments (3/18/212), and 4 weeks post-qGLT (4/22/19). The results are based on low-resolution electromagnetic tomography analyses (LORETA) obtained from the Neuronavigator 3.06/.07 programs (Applied Neuroscience, Inc.). Current density was measured at $\sim$7600 locations including all cortical areas, hippocampus, amygdala, and insular cortex for frequencies between 1 and 30 Hz. Results were compared with a lifespan normative database in terms of *Z*-score deviations.[26] Connectivity measures for coherence were obtained for frequency bands including delta, theta, low and high alpha, total alpha, low middle and high beta, and overall beta from 12 to 25 Hz.

qEEG findings

Baseline linked ears and Laplacian power spectral analyses showed excessive power in EC and EO conditions, bilaterally in frontal, temporal, and parietal areas over a wide frequency range. The patient's EEG amplitude asymmetry, coherence, and EEG phase deviated from the norm in frontal, temporal, parietal, and occipital relations. LORETA three-dimensional source analyses were consistent with the surface EEG.

Importantly, elevated LORETA current sources were present in four clinically relevant areas that corresponded to the patients clinical presentation:

1. Brodmann area (BA) 21 (5 Hz), which is associated with recognition of known faces.[27]
2. BA 38 at (6 Hz), which is among the earliest affected by AD, and at the start of TLE.[27]
3. BA 45 (7 Hz), which is associated with face encoding.[27]
4. Left hippocampus (Figs. 1–3), which is associated with memory encoding deficits and AD.

Diagnostic reasoning

The patient presented with history and complaints consistent with AAP, TLE, and MCI, with postmenopausal exacerbation. APOE status, memory, word finding complaints, and strong family history suggested she was in the early clinical phase of AD. Symptomatology correlated with the abnormal qEEG findings.

As a mitochondrial energy deficit is a pathophysiological feature of AD,[22] we hypothesized that provision of energy through PBM to specific dysfunctional cortical areas, as determined by qEEG, might mitigate the patient's MCI. We did not anticipate normalization of AAP or TLE.

Treatment

The patient initially underwent a thorough work-up to detect any treatable metabolic factors that might be contributory to her conditions, the correction of which might promote improved brain function. The areas assessed included lifestyle factors (sleep, social status, and socioeconomic condition), diet, nutritional deficits, immune and infectious conditions, hormonal status, genetics, and toxicology. These items were addressed over the course of 6 months, and resulted in significant clinical improvements, however, deficits, both subjective (impaired facial recognition, distractibility, and memory deficits) and on qEEG, remained.

Clearance for qGLT is determined by MRI and/or MRA to rule out anomalies (e.g., cysts, tumors, and vascular) that could be destabilized by heat, volume changes, or increased vascular flow. After informed consent, the patients' hair was shaved/removed down to the scalp in the areas to be treated to reduce light absorption by hair. BAs showing dysfunction (particularly those correlating with symptoms) were mapped to scalp areas using a standard 10/20 cap, and each area of treatment was measured (cm^2). An Aspen Pinnacle diode laser (810 nM, collimated, 3 cm wide beam aperture, spot size 7.065 cm^2; https://www.aspenlaser.com/pinnacle-laser-series) was applied directly to clean skin. Using oscillation across individual treatment areas, fans, and pauses in irradiation, we were able to maintain normal skin temperature.

Treatment parameters that varied over the course of 25 thrice weekly treatment sessions were fluence (5–60 J/cm^2), power (5–25 W), power density (0.354–0.177 W/cm^2), and dosage per location (110–4000 J). Pulse frequency remained constant at 10 Hz (see Supplementary Appendix SA and Supplementary Appendix SB). Our target dose for mitochondrial activation is 1–2 J/cm^2. Assuming 2.4–2.9% light penetration to the cortex,[24] the minimum (1 J/cm^2) target dose for a given area was calculated by the formula:

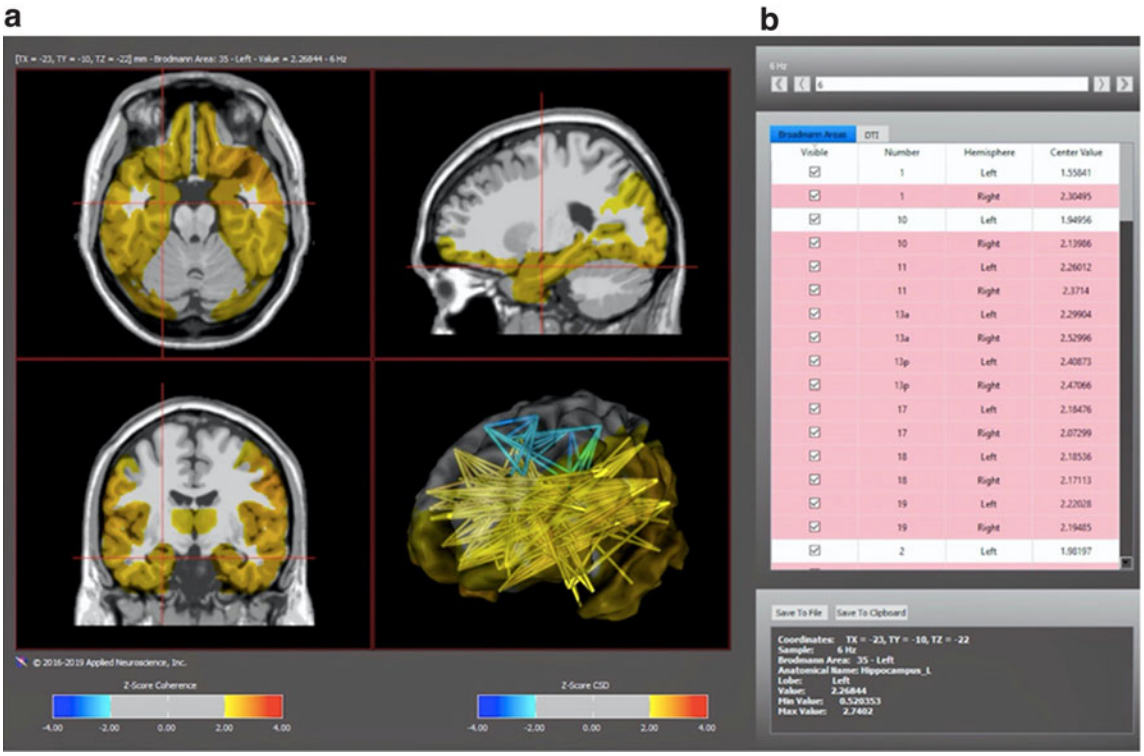

FIG. 1. **(a)** (1/4/19, baseline EO, top) shows excessive CD *Z*-scores in many temporal lobe locations bilaterally, as well as frontal and occipital lobes. The highest deviation was in the left hippocampus with the value of 2.7326. The fourth panel shows a complex pattern of hypocoherence (blue) and hypercoherence (yellow and orange) between many areas. **(b)** (1/4/19 baseline, EC bottom) shows the left hippocampal value at 2.26844 *Z*-scores. CD, current density; EC, eyes closed; EO, eyes open.

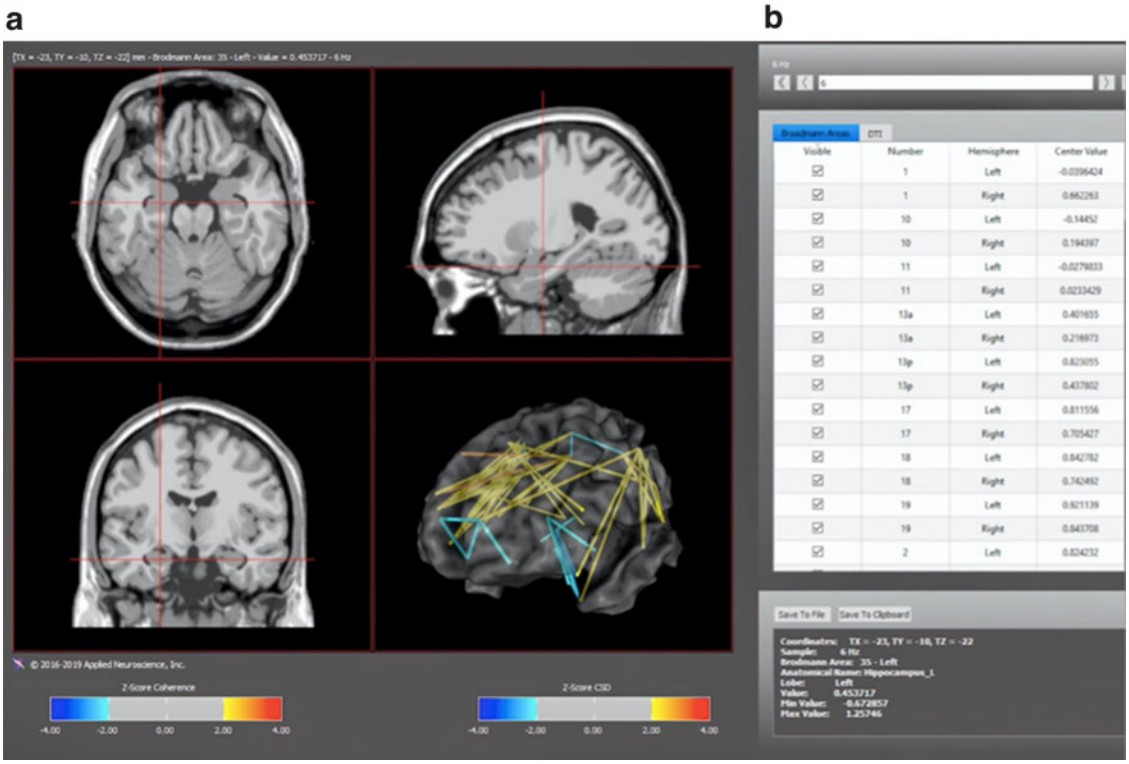

FIG. 2. **(a)** (4/22/19, EO, top) shows the CD values are normal with the left hippocampus *Z*-score at 0.45317, illustrating continuing improvement after treatment. There are somewhat increased number of hypocoherence values but decreased hypercoherence values compared with the previous EO recording. **(b)** (4/22/19, EC, bottom) shows the left hippocampus exhibits a normal *Z*-score of 1.76733.

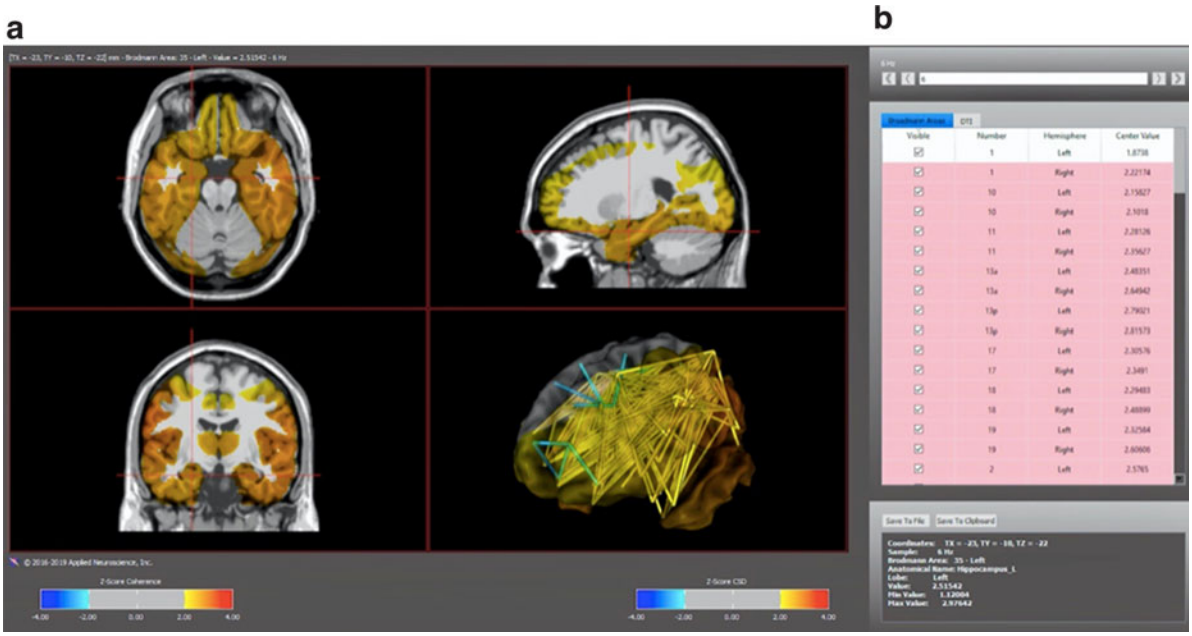

FIG. 3. **(a)** (7/26/19, EO, top) shows mild to moderate increased CD bilaterally in temporal lobe locations. However, *Z*-score for the left hippocampus remains in the normal range with the value of 1.85711. There is still considerable hypo- and hypercoherence at many locations similar to those seen previously. **(b)** (7/26/19, EC, bottom) shows regression with increased CD in temporal, orbitofrontal, and occipital locations bilaterally. The left hippocampus has a *Z*-score value of 2.51542. There are somewhat fewer areas of hypocoherence compared with previous recordings but increased hypercoherence as illustrated by yellow connectivity lines.

$J = cm^2/2.65 \times 100$. Initial placebo treatment was followed on the next visit by 25% of the target dose per area. The critical parameters and adjustments to treatment involved location, which was based on qEEG findings correlated with symptoms, and dose (J/cm^2) that was based on the response to the last treatment. At each visit, dose was adjusted downward for adverse response such as headache, excess fatigue, upward if no response, and maintained if good response. Power was adjusted upward to reduce treatment delivery time when large surface areas were treated, while assuring skin temperature remained comfortable.

The baseline qEEG indicated numerous BAs with current source values >1.65 standard deviations (*Z*-scores) from the norm, with BAs 21, 38, 43, and 45 having particular correspondence to the patients symptomatology. This information was used to target the scalp locations corresponding to those specific areas. Table 1 documents changes in *Z* score values (left and right) in Delta band (1–4 Hz) in specific BAs at baseline (1/4/19), after 21 treatments (3/18/19), and 4 weeks (4/22/19) post-treatment. Because the qEEG *Z*-scores were normalized in the areas of concern, and the patient became asymptomatic, treatment was discontinued.

Tolerability

The patient reported that the effect was rapid, cumulative, and required application three times per week for optimal results. Tolerability was excellent.

Results

Objective data

The qEEG results (Figs. 1–3 and Table 1), subjective experience, and clinical assessment consistently indicated improvement. There was surprising subjective resolution of

TABLE 1. CHANGES IN *Z* SCORE VALUES LEFT (L) AND RIGHT (R) IN DELTA BAND (1–4 HZ) IN SPECIFIC BRODMANN AREAS AND THE HIPPOCAMPUS (HIPPO) AT BASELINE (1/4/19), AFTER 21 TREATMENTS (3/18/19), AND 4 WEEKS POST-TREATMENT (4/22/19)

	1/04/19 EO	*1/04/19 EC*	*3/18/19 EC*	*3/18/19 EO*	*4/22/19 EO*	*4/22/19 EC*
BA 21	2.58L/2.57R	2.00L/2.28R	1.03L/1.36R	1.33L/1.29R	–0.96L/–0.80R	–0.128L/–0.16R
BA 38	2.42L/2.52R	1.74L/2.21R	0.77L/1.06R	1.18L/0.98R	–1.03L/–1.28R	–0.35L/–0.53R
BA 43	2.44L/2.60 R	1.81L/2.27R	0.85L/1.43R	1.32L/1.33R	–0.91L/–1.16R	–0.35L/–0.37R
BA 45	2.34L/2.10R	1.57L/1.80R	0.73L/0.81R	1.30L/0.83R	–1.09L/–1.34R	–0.39L/–0.45R
Hippo	2.50L/2.49R	1.89L/2.23R	1.00L/1.37R	1.36L/1.11R	–0.90L/–1.40R	–0.10L/–0.48R

EO and EC values for each date. Normalization of *Z*-scores and symptoms (03/18/19) resulted in termination of treatment. Gray shaded areas reflect abnormal *Z*-scores. The single darker gray cell reflects an ipsilateral abnormality. Note the post-treatment trajectory of *Z*-scores to a nadir in the 4/22/19 recording. *Z* scores beyond ±1.65 are considered abnormal.

BA, Brodmann area; EC, eyes closed; EO, eyes open.

prosopagnosia after the first treatment, with no additional episodes reported. The post-treatment Cambridge Face Memory Test[28] score (8/1/19) was 52 (average young adult score is 58 ± 7.34 SD). The qEEG at 4 weeks post-treatment showed additional improvement. One possible seizure event occurred 4 months post-treatment. The left hippocampal *Z*-score, 4 weeks after treatment, was completely normalized ($Z = 0.45317$, baseline $Z = 2.7326$).

Subjective

Reported through email after first treatment: ''After I left a client's home in the afternoon, I realized 'I can remember the client'—I could visualize his face, body, height, and... I would be able to pick him out of a crowd. Shocking. It's been so long since I had facial recognition like that. Yesterday I did an audit, and I can remember the husband's face. Today I did an audit and I can remember what the person looks like.''

4th treatment: ''There is definitely better facial recognition. I watched a movie last night and I can remember the actress's face, the 2 moles on her face.''

13th treatment: ''My memory improvement is occurring at such a rate that I am regaining memory capacity I never realized I had lost. Now people call me 2–3 weeks after an order, and I can remember what we discussed 2–3 weeks ago.''

23rd treatment: ''My brain has changed.''

At 16 weeks post-treatment (7/26/19) the patient reported: ''I don't feel the facial recognition is a problem anymore. I made more money this year, so far, than in all of 2017.'' Despite these improvements, she felt there was some regression, and she felt that ''the treatments were terminated prematurely.''

Discussion

This is the first report of the successful reversal of AAP, which was achieved using qGLT, taking into consideration tissue and location-specific needs and response, with treatment-by-treatment optimization of parameters. To our knowledge, this is the first case report indicating that qGLT may be useful as an approach to TLE, and may provide a pathway for normalization of hippocampal function as assessed by qEEG/LORETA and subjective assessment in those with MCI.

The 4/22/19 qEEG showed that improvement progressed for at least 4 weeks after qGLT, but there was some nonclinical reversal (although AAP, TLE, and MCI remained in remission) at 17 weeks post-treatment. We hypothesize that in the absence of ongoing qEEG guided laser treatment (qLGT), pathophysiological processes reasserted their dominance (APOE-4 pathophysiology).

The strengths in this approach are that objective data were obtained at multiple time points, which mirrored subjective and functional changes. The primary limitation of this report is that it is a single case, and results may not be generalizable. Because there are multiple diagnoses involved, we questioned whether AAP was an incorrect diagnosis, and that perhaps her inability to recall faces might be due to TLE superimposed on early memory loss related to an early Alzheimer's process. The patient's trouble tracking faces in movies, whose content was otherwise recalled, argues against this hypothesis. Since the Cambridge Face Recognition test was not done at baseline, the degree of improvement was not quantified, with diagnosis and response being reliant on the subjective report. In addition, the diagnosis of TLE relied on the suggestive qEEG signature along with clinical symptoms.

Conclusions

We conclude that the use of qGLT, when layered on modification of lifestyle, nutrition, and hormone therapy, was effective in reversing AAP, markedly reducing TLE, and normalizing MCI and hippocampal function in an APOE-4 homozygote. The normalization of hippocampal function indicates that the qGLT impacted a deep brain structure, likely in an indirect manner. The time course of sustained neuronal improvement as measured by qEEG extends at least 4 weeks beyond termination of treatment. With a lack of effective treatments for AAP, this report justifies additional study of qGLT in the treatment of AAP.

Authors' Contributions

R.H. collected patient information, conceptualized, designed, and performed treatment interventions based on qEEG analysis, performed laboratory testing, and drafted the article. J.L. assisted with data analysis and figures. All authors have seen and approved this article.

Acknowledgments

We are grateful to the patient for allowing us to publish this case report. We acknowledge the generosity of Aspen Laser who provided the laser, and Todd Penberthy, PhD, for assisting with editing the article.

Ethics Statement

This study was carried out with the informed consent of the patient regarding the experimental nature of the treatment. Clinical data in this case report were collected in the normal course of treatment. Written consent from the patient was given for the publication of this case report.

Author Disclosure Statement

No competing financial interests exist. The methodology is patent pending.

Funding Information

There was no funding received for this study.

Supplementary Material

Supplementary Appendix SA
Supplementary Appendix SB

References

1. Barton JJ. Structure and function in acquired prosopagnosia: lessons from a series of 10 patients with brain damage. J Neuropsychol 2008;2:197–225.
2. DeGutis JM, Chiu C, Grosso ME, Cohan S. Face processing improvements in prosopagnosia: successes and failures over the last 50 years. Front Hum Neurosci 2014;8:561.

3. Corrow SL, Dalrymple KA, Barton JJ. Prosopagnosia: current perspectives. Eye Brain 2016;8:165–175.
4. Bate S, Bennetts RJ. The rehabilitation of face recognition impairments: a critical review and future directions. Front Hum Neurosci 2014;8:491.
5. DeGutis JM, Cohan S, Alexander DK, Aguirre GK, Nakayama K, editors. Facial expression training improves emotion recognition and changes neural tuning in a patient with acquired emotion recognition deficits and prosopagnosia. Vision Sciences Society Annual Meeting, Naples, Florida, 2013.
6. Davies-Thompson J, Fletcher K, Hills C, Pancaroglu R, Corrow SL, Barton JJ. Perceptual learning of faces: a rehabilitative study of acquired prosopagnosia. J Cogn Neurosci 2017;29:573–591.
7. Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L. Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: case series report. Photomed Laser Surg 2017;35:432–441.
8. Berman MH, Halper JP, Nichols TW, Jarrett H, Lundy A, Huang JH. Photobiomodulation with near infrared light helmet in a pilot, placebo controlled clinical trial in dementia patients testing memory and cognition. J Neurol Neurosci 2017;8:176.
9. Zomorrodi R, Saltmarche, A.E., Loheswaran, G., Ho, K.F. and Lim, L., eds. Complementary EEG evidence for a significantly improved Alzheimer's disease case after photobiomodulation treatment. 26th Annual Scientific Conference, Canadian Academy of Geriatric Psychiatry, Toronto, 2017.
10. Chao LL. Effects of home photobiomodulation treatments on cognitive and behavioral function, cerebral perfusion, and resting-state functional connectivity in patients with dementia: a pilot trial. Photobiomodul Photomed Laser Surg 2019;37:133–141.
11. Santos L, Olmo-Aguado SD, Valenzuela PL, et al. Photobiomodulation in Parkinson's disease: a randomized controlled trial. Brain Stimul 2019;12:810–812.
12. das Neves MF, Aleixo DC, Mendes IS, et al. Long-term analyses of spastic muscle behavior in chronic poststroke patients after near-infrared low-level laser therapy (808 nm): a double-blinded placebo-controlled clinical trial. Lasers Med Sci 2020;35:1459–1467.
13. Morries LD, Cassano P, Henderson TA. Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. Neuropsychiatr Dis Treat 2015;11:2159–2175.
14. Yao X, Liu C, Feng D, Yin J, Chen G. Transcranial near-infrared laser therapy in improving cognitive recovery of function following traumatic brain injury. Curr Neuropharmacol 2018;16:1320–1326.
15. Henderson TA, Morries LD. SPECT perfusion imaging demonstrates improvement of traumatic brain injury with transcranial near-infrared laser phototherapy. Adv Mind Body Med 2015;29:27–33.
16. Naeser MA, Hamblin MR. Traumatic brain injury: a major medical problem that could be treated using transcranial, red/near-infrared LED photobiomodulation. Photomed Laser Surg 2015;33:443–446.
17. Lapchak PA, Boitano PD, Butte PV, et al. Transcranial near-infrared laser transmission (NILT) profiles (800 nm): systematic comparison in four common research species. PLoS One 2015;10:e0127580.
18. Henderson TA, Morries LD. Multi-watt near-infrared phototherapy for the treatment of comorbid depression: an open-label single-arm study. Front Psychiatry 2017;8:187.
19. Naeser MA, Zafonte R, Krengel MH, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. J Neurotrauma 2014;31:1008–1017.
20. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol B 1999;49:1–17.
21. Serrage H, Heiskanen V, Palin WM, et al. Under the spotlight: mechanisms of photobiomodulation concentrating on blue and green light. Photochem Photobiol Sci 2019;18:1877–1909.
22. Blonz ER. Alzheimer's disease as the product of a progressive energy deficiency syndrome in the Central Nervous System: the neuroenergetic hypothesis. J Alzheimers Dis 2017;60:1223–1229.
23. Tedford CE, DeLapp S, Jacques S, Anders J. Quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue. Lasers Surg Med 2015;47:312–322.
24. Henderson TA, Morries LD. Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain? Neuropsychiatr Dis Treat 2015;11:2191–2208.
25. Luo M, Zhou XH, Zou T, Keyim K, Dong LM. Type II deiodinase polymorphisms and serum thyroid hormone levels in patients with mild cognitive impairment. Genet Mol Res 2015;14:5407–5416.
26. Thatcher RW. Handbook of Quantitative Electroencephalography and EEG Biofeedback. St. Petersburg, FL: Anipublishing, 2012.
27. Technologies TC. Cortical Functions, McLean Hospital, Harvard Medical School, Wellesley College. Available at: testmybrain.org. 2012.
28. Duchaine B, Nakayama K. The Cambridge Face Memory Test: results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants. Neuropsychologia 2006;44:576–585.

Address correspondence to:
Robert Hedaya, MD
The Whole Psychiatry & Brain Recovery Center
Institute for Functional Medicine
Georgetown University School of Medicine
Rockville, MD
USA

E-mail: rhedayamd@yahoo.com

Received: April 15, 2021.
Accepted after revision: October 4, 2021.
Published online: December 31, 2021.