Significant Improvement in Cognition after Transcranial and Intranasal Photobiomodulation: A Controlled, Single-Blind Pilot Study in Participants with Dementia

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ABSTRACT

Introduction: This controlled, single-blind, pilot study investigated if transcranial and intranasal photobiomodulation (PBM) therapy in the near-infrared (NIR) 810nm wavelength, could improve cognition in dementia. Methods The light-emitting diode (LED) devices for PBM were engineered to target cortical nodes of the Default Mode Network (DMN) that are dysregulated in Alzheimer's disease. Nineteen participants were randomized into a 12-Week Active or Sham treatment series, with a 4-Week, No-Treatment follow-up. Patients were assessed with MMSE and ADAS-cog tests. The protocol involved weekly, in-clinic use of a combined transcranial-plus-intranasal PBM device; and daily at-home intranasal-only PBM device. Results Participants with moderate-severe impairment (Baseline MMSE 5-24) receiving Active treatment showed significant ($p<0.03$) improvements on assessment scores after 12 weeks. They reported better sleep, fewer angry outbursts, less anxiety and less wandering. After the 4-Week, No-Treatment follow-up, some declines were noted. Participants with mild impairment (Baseline MMSE 25-30) in both the Active and Sham groups showed no significant improvements in their scores. No adverse events were related to the treatments. Conclusion Results from this controlled study are the first to report significant cognitive improvement in dementia participants following PBM treatments. They suggest future large scale controlled studies are warranted. The safety, low-cost and ease of transcranial-intranasal NIR LED application show potential for long-term home treatments. No study-related adverse events occurred.

INTRODUCTION

- **Photobiomodulation (PBM) therapy is safe, non-invasive based on research dating back to the 1960's PBM or low-level laser (or light) therapy (LLLT) uses either visible red or nearinfrared (NIR) light to stimulate, heal, and repair damaged or dying cells or tissues**
- **Mechanisms of action involve the stimulation of mitochondria as well as a biochemical response resulting in down stream systemic effects.**
- **PBM is applicable to a diverse range of brain diseases and injury using transcranial PBM (tPBM) Acute stroke was the first area to be tested with PBM**
- **tPBM can penetrate to a depth of 40-55mm, from scalp application location**
- **Traumatic brain injury has been investigated in animal and human subjects where significant improvements in executive function and verbal memory were observed**
- **Psychiatric disorders (depression and anxiety) have also been investigated in clinical studies where significant benefits were also observed**
- **tPBM have shown positive outcomes in mouse models of Alzheimer's disease (AD) and Parkinson's disease**
- **AD originates in the lateral entorhinal cortex of the hippocampus, with progression, there is also functional dysregulation of the Default Mode Network (DMN) which includes the bilateral hippocampus (entorhinal cortex), mesial prefrontal cortex (mPFC), precuneus/posterior cingulate cortex (precun/pCC), and inferior parietal lobe (angular gyrus). Hence, treatment of cortical nodes in the DMN would be a primary treatment goal, in patients with MCI, dementia or AD. See Figure 1d. In this study, the light-emitting diode (LED) devices were designed to deliver nearinfrared photons transcranially and intranasally, to the cortical nodes in the DMN.**

- **The objectives of this pilot study were 1) to determine the feasibility of PBM for improving cognition and QoL in dementia; and 2) to evaluate the LED device performance and protocol, in preparation for a larger randomized, double-blind, controlled research study.**
- **This is the first randomized, controlled clinical study with PBM.**

METHODS

This controlled, single-blind, pilot study investigated if transcranial and intranasal photobiomodulation (PBM) therapy in the near-infrared (NIR) 810nm wavelength, could improve cognition in dementia. Methods The light-emitting diode (LED) devices for PBM were engineered to target cortical nodes of the Default Mode Network (DMN) that are dysregulated in Alzheimer's disease. Nineteen participants were randomized into a 12-Week Active or Sham treatment series, with a 4-Week, No-Treatment follow-up. Patients were assessed with MMSE and ADAS-cog tests. The protocol involved weekly, in-clinic use of a combined transcranial-plus-intranasal PBM device; and daily at-home intranasal-only PBM device. Results Participants with moderate-severe impairment (Baseline MMSE 5-24) receiving Active treatment showed significant ($p<0.03$) improvements on assessment scores after 12 weeks. They reported better sleep, fewer angry outbursts, less anxiety and less wandering. After the 4-Week, No-Treatment follow-up, some declines were noted. Participants with mild impairment (Baseline MMSE 25-30) in both the Active and Sham groups showed no significant improvements in their scores. No adverse events were related to the treatments. Conclusion Results from this controlled study are the first to report significant cognitive improvement in dementia participants following PBM treatments. They suggest future large scale controlled studies are warranted. The safety, low-cost and ease of transcranial-intranasal NIR LED application show potential for long-term home treatments. No study-related adverse events occurred. INTRODUCTION

• The results have been reported in two sub-groups based on severity of the MMSE baseline scores: - Moderate-to-severe sub-group (scores 5-24), - Normal to mild sub-group (scores 25-30).

• In the baseline MMSE 5-24 sub-group, mean (SD) scores on the MMSE for the 7 participants who completed treatment in the Active group increased from 14 (8.1) to 16 (9.0), an improvement of 2 points on average ($p=0.03$, 2-tailed paired t-test). Similarly, ADAS-cog scores decreased from 42.2 (20.7) to 37.2 (21.1), an improvement of 5 points on average ($p=0.03$, 2-tailed paired t-test). The only participant in this moderate-severe sub-group randomized to receive Sham treatment dropped out before post-baseline assessment so a between-group comparison was not possible.

• Improvements were also seen in the normal to mild subgroup (MMSE 25-30). In particular, MMSE scores for the 5 participants who completed Active treatment increased from 27 (1.0) to 28.8 (1.3). However, due to small sample size this improvement was not statistically significant.

• After the "4-Week, No Treatment" period, 4/6 of the participants (all moderatesevere) worsened relative to their MMSE scores after 12 Weeks of Active treatment. Also, 5/6 of these participants (all moderate-severe) worsened after the "4-Week NoTreatment" period relative to their ADAS-cog scores after 12 Weeks of Active treatment.

RESULTS SUMMARY

• PBM treatments for moderate-severe cognitive impairment can result in significant quantitative and qualitative improvements • This non-invasive treatment strategy may provide a safer, more effective alternative to conventional treatments • The declines observed during the final 4-Week No-Treatment period indicate that the treatment needs to be continued on a regular basis to maintain the benefits of PBM • PBM

devices for this application can be amenable to home use thereby increasing client/ family flexibility and control, broadening accessibility to treatment and decreasing costs • It can improve or maintain memory and cognitive abilities, and positively influence the QoL of those afflicted as well as their caregivers • It is the first, controlled study to report significant improvement in cognition for dementia patients following a series of NIR PBM treatments • Future, large scale controlled studies are warranted • The safety, ease of use and cost effectiveness of transcranial-intranasal NIR PBM shows promise for long-term home treatment of dementia.

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1. Chung H, Dai T, Sharma SK, et al. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. 2012;40(2):516-33. 2. Naeser MA, Hamblin MR. Potential for Transcranial Laser or LED Therapy to Treat Stroke, Traumatic Brain Injury, and Neurodegenerative Disease. Photomed Laser Surg. 2011;29(7):443-6. 3. Lapchak PA. Transcranial near-infrared laser therapy applied to promote clinical recovery in acute and chronic neurodegenerative diseases. Expert Rev Med Devices. 2012;9(1):71-83. 4. Rojas JC, Gonzalez-Lima F. Neurological and psychological applications of transcranial lasers and LEDs. Biochem Pharmacol. 2013;86(4):447-57. 5. Ando T, Xuan W, Xu T, et al. Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice. PLoS ONE. 2011;6(10):e26212-20. 6. De Taboada L, Yu J, El-Amouri S, et al. Transcranial laser therapy attenuates amyloid-beta peptide neuropathology in amyloid-beta protein precursor transgenic mice. J Alzheimers Dis. 2011;23(3):521-35. 7. Purushothuman S, Johnstone DM, Nandasena C, et al. Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex – evidence from two transgenic mouse models. Alzheimers Res Ther. 2014;6(1):2. 8. Johnstone DM, Mitrofanis J, Stone J. Targeting the body to protect the brain: inducing neuroprotection with remotely-applied near infrared light. Neural Regen Res. 2015;10(3):349-51. 9. Farfara D, Tuby H, Trudler D, et al. Low-level laser therapy ameliorates disease progression in a mouse model of Alzheimer's disease. J Mol Neurosci. 2015;55(2):4306. 10. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci. 2009;29:1860–73. 11. Raichle ME. The Brain's Default Mode Network. Annu. Rev. Neurosci. 2015;38:413–27.

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• The deterioration in the MMSE and ADAS-cog scores in the majority of the moderate-severe cases, after the 4-Week No-Treatment phase is supportive of the positive, significant improvements present after the 12 weeks of Active PBM

• In the mild impairment sub-group (Baseline MMSE 25-30) the difference between Active treatment and Sham was not significant. This may be related to improvements in two of the Sham participants relative to the small sample size of the study

• The improvements in the two Sham participants could be due to artificially low baseline scores - due a surgical procedure and a history of depression in one case; and anxiety about strong family history of AD coupled with recent MCI diagnosis in the other. Both were more relaxed and so scored better in later tests

• In the Active group, participants reported positive psychological changes or feelings; and memory improvements. Their caregivers reported fewer angry outbursts and decreased anxiety and fretting, less wandering and more communications and responses at home and in family gatherings

• The sleep patterns of the Active participants improved, resulting in enhanced quality and quantity of their sleep.

Recommendations for future studies • Avoid discontinuation of Active PBM once it has started, especially in progressive, neurodegenerative diseases such as MCI and AD • Consider home PBM combined with telemetry and video conferencing to monitor treatments (after initial in-person training), and in-person clinic visits would only be necessary for cognitive assessments • Consider adding other standardized methods of documenting other potential changes - i.e., improved sleep, communication and social interaction; decreased anxiety, depression and disruptive behaviors (angry outbursts, physical aggression or wandering). Additionally, measuring caregiver impact and understanding their life experience helps to understand the full impact of PBM for all those involved • Closely monitor changes in patient health because they influence outcome measures • Provide PBM for the caregivers too because they benefitted from improved sleep, sharper memory, less anxiety. This gives them greater capacity to cope with the day-to-day challenges of being a caregiver.

DISCUSSION

Anita E. Saltmarche RN, MHSc 1, Margaret A. Naeser PhD 2, Kai Fai Ho PhD 3, Michael R. Hamblin PhD 4,5,6, Lew Lim DNM, PhD, MBA 7 1. Saltmarche Health & Associates Inc. Mono, Canada, 2. Boston University School of Medicine, Boston MA USA, 3. STAT-TU Inc., Toronto, ON, Canada, 4. Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA, 5. Harvard Medical School, Boston, MA, USA, 6. Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, USA, 7. Vielight Inc., Toronto, ON, Canada

Significant Improvement in Cognition after Transcranial and Intranasal Photobiomodulation: A Controlled, Single-Blind Pilot Study in Participants with Dementia

Design This pilot study was a randomized, single-blind, placebo-controlled study.

Participants • 19 participants were randomized in a 2:1 ratio - 13 in Active group, 6 in Sham group • Participants ranged between 64-90 years • Time between diagnosis of dementia and participation - in the study ranged from 6 months to 20 years. See Table 2 • All participants also reported deficits in memory, cognition, functional or work-related declines at the commencement of the study.

Cognitive Outcome Measures • MMSE and ADAS-cog assessment scales were used • Participants were tested at: Baseline (Week 0), Week 6 (mid- treatment), Week 12 (end of treatment), and at the end of a "4-Week, No-Treatment" follow-up period • Qualitative comments were documented in a "Daily Home Treatment Journal".

PBM Therapy Devices and Treatment Method • An intranasal-only "810" device (Fig. 1a), used only at home, consisted of one diode, that emitted NIR light of 810 nm wavelength, pulsed at 10 Hz, 50% duty cycle. It shut off automatically after 25 minutes of treatment time. This device was used daily for 12 weeks, excluding days participants had clinic appointments for treatment with the "Neuro" device. • The "Neuro" device consisted of a headset frame, holding four separate LED cluster heads plus one intranasal LED. All diodes emitted light of 810 nm wavelength, synchronized to pulse at 10 Hz, 50% duty cycle. See Figs. 1b and c. The device shut off automatically after 20 minutes of treatment time (rechargeable). Each of the four LED cluster heads on the headset contained 3 diodes. The "Neuro" was used 2x/week during in-clinic office visits for the first 2 weeks, and then applied only 1x/ week, for each of the next 10 weeks.

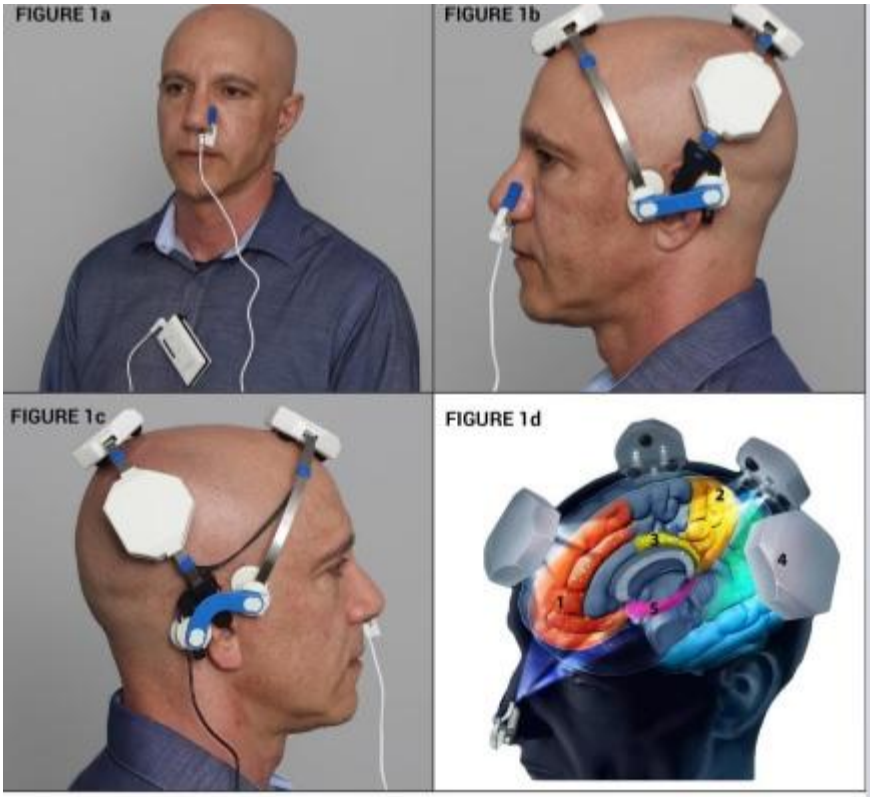

FIGURE 1.

1a "Vielight 810"
1b "Vielight Neuro", Left view
1c "Vielight Neuro", Right view
1d Targeted Default Mode Network Nodes :

1. Mesial Prefrontal Cortex
2. Precuneus
3. Posterior Cingulate Cortex
4. Inferior Parietal Lobe
5. Hippocampus

RESULTS

• The results have been reported in two sub-groups based on severity of the MMSE baseline scores: - Moderate-to-severe sub-group (scores 5-24), - Normal to mild sub-group (scores 25-30).

• In the baseline MMSE 5-24 sub-group, mean (SD) scores on the MMSE for the 7 participants who completed treatment in the Active group increased from 14 (8.1) to 16 (9.0), an improvement of 2 points on average (p=0.03, 2-tailed paired t-test). Similarly, ADAS-cog scores decreased from 42.2 (20.7) to 37.2 (21.1), an improvement of 5 points on average (p=0.03, 2-tailed paired t-test). The only participant in this moderate-severe sub-group randomized to receive Sham treatment dropped out before post-baseline assessment so a between-group comparison was not possible.

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worsened after the "4-Week NoTreatment" period relative to their ADAS-cog scores after 12 Weeks of Active treatment.

TABLE 2. MMSE and ADAS-cog Scores

Subject Number	MMSE				ADAS-cog			
	Baseline	Week 6	Week 12	4-Week No Treatment	Baseline	Week 6	Week 12	4-Week No Treatment
Active Treatment								
103	5	7	8	1	57	60	59	63.67
116	6		— Dropped Out —		53.67		— Dropped Out —	
117	6	6	4	7	61	63	57.67	59.67
115	10	11	13	11	58	52	50	52
119	10	13	12	Missed	58	46	48.67	Missed
101	21	27	23	20	26.33	9.33	16.66	22
113	22	23	24	25	20.67	15.66	13.33	14
109	24	25	28	25	14.33	17.34	15.00	12.33
105	26*	25	27	24	12	16.34	15.33	13.33
114	26*	27	30	26	18.33	13	13.33	13.66
110	27*	28	29	27	14.67	7	10	11.67
104	28*	30	30	30	8	9.33	5.66	5
112	28*	29	28	30	15.34	9.33	12.67	10
Sham Treatment								
106	18		— Dropped Out —		25.33		— Dropped Out —	
102	25	28	28	28	15.66	16	12	12.33
111	25	26	26	25	22.67	21.67	16	15
107	28*	28	30	30	6.34	9.33	9	5
108	29*		— Dropped Out —		7.33		— Dropped Out —	
118	30*	30	30	30	11.34	6.67	4.34	1.33

*MMSE score above 24, but diagnosed with MCI, dementia or AD and symptoms affecting quality of life. MMSE – Mini Mental State Exam, ADAS-cog - Alzheimer's Disease Assessment Scale- Cognitive Subscale

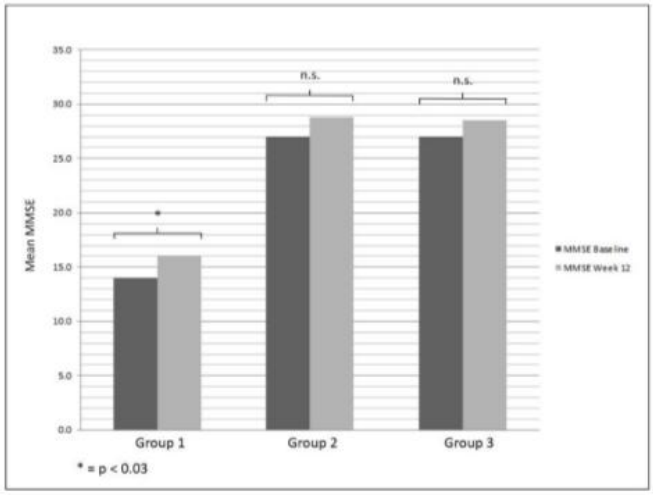

FIGURE 2a. Changes in MMSE scores over 12 weeks.

Group 1. Baseline MMSE score of 5 to 24 (Active Intervention)

Group 2. Baseline MMSE score of 25 to 30 (Active Intervention)

Group 3. Baseline MMSE score of 25 to 30 (Sham Intervention)

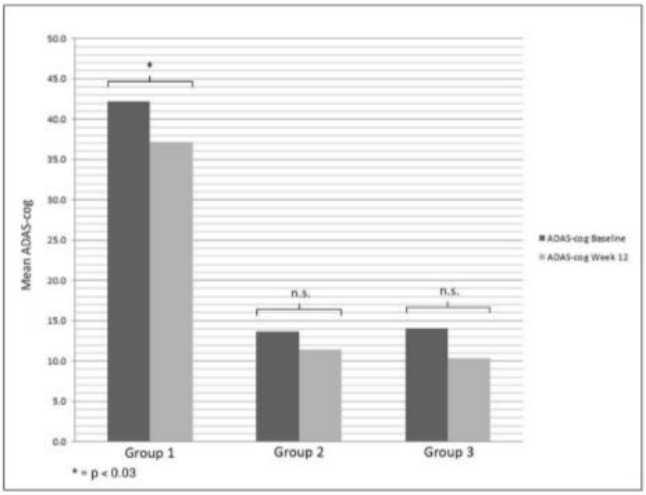

FIGURE 2b. Changes in ADAS-cog scores over 12 weeks.

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SUMMARY

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• PBM devices for this application can be amenable to home use thereby increasing client/ family flexibility and control, broadening accessibility to treatment and decreasing costs

• It can improve or maintain memory and cognitive abilities, and positively influence the QoL of those afflicted as well as their caregivers

• It is the first, controlled study to report significant improvement in cognition for dementia patients following a series of NIR PBM treatments

• Future, large scale controlled studies are warranted

• The safety, ease of use and cost effectiveness of transcranial-intranasal NIR PBM shows promise for long-term home treatment of dementia.

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