A Pilot Clinical Trial of Transcranial and Intranasal Photobiomodulation for Cognitive and Behavioral Function, Cerebral Perfusion, and Resting State Functional Connectivity

Linda L. Chao, Ph.D.

University of California, San Francisco & San Francisco VA Medical Center

P2-018

Poster #23665

INTRODUCTION

- Photobiomodulation (PBM) describes the use of radiant light energy to modify biological functions or to induce a therapeutic effect in a non-thermal manner.[1]
- PBM can be delivered transcranially to target the brain parenchyma in humans because near infrared (NIR) wavelengths of light (λ=750-950 nm) can penetrate the scalp and skull to reach a depth of 40-50 mm in the brain.[2]
- A case series report[3] published last year described improved cognitive function in 5 patients with dementia after 12 weeks of transcranial and intranasal PBM treatments.
- This study sought to **replicate** and **expand** upon the findings of Saltmarche et al.[3] by investigating the effects of 12 weeks of **home** transcranial and intranasal **PBM treatments** on 1) **cognitive function**, 2) **behavioral symptoms**, 3) **cerebral perfusion**, and 4) **resting state functional connectivity** in 8 patients with **dementia**.

METHODS

- Eight older adults who had been diagnosed with dementia by their physicians participated in the study (see table below for baseline characteristics).
- Half the participants were assigned to 12 weeks of PBM treatments while half were assigned to 12 weeks of Usual Care (UC).

Baseline Characteristics of Study Participants

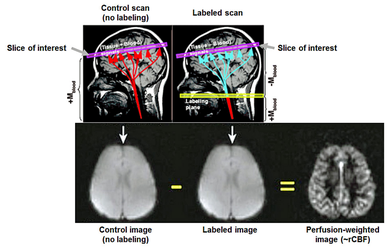
	PMB (n=4)	UC (n=4)	*t*-value[a]	*p*-value
No. female (%)	3 (75%)	2 (50%)	--	1.00[b]
Age, years	80.5 (6.5)	79.0 (5.9)	0.34	0.74
Education, years	18.5 (1.9)	18.0 (1.6)	0.40	0.71
Race, White	4 (100%)	4 (100%)	--	1.00[b]
Baseline MMSE	19.5 (7.0)	22.3 (1.3)	0.77	0.47
Baseline ADAS-cog	37.5 (11.0)	32.1 (0.7)	0.98	0.40
Baseline NPI	34.0 (23.5)	10.5 (3.7)	2.09	0.08

[a] $df = 6$
[b] p-value from Fisher's Exact Test
MMSE: Mini-Mental State Examination;[4] ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognitive Subtest;[5] NPI: Neuropsychiatry Inventory[6]

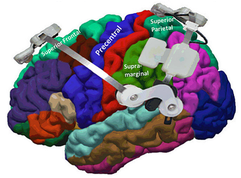
- PBM treatments were administered by the participants' study partners (i.e., family members) at home with a commercially available PBM device (Vielight Neuro Gamma, below) every other day for 12 weeks.

METHODS (cont.)

- Behavioral outcome measures were assessed at **baseline, 6-weeks, and 12-weeks**.
  - Cognitive function was assessed with the **Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)**.[5] Scored according to the number of errors that the participant makes, a **lower ADAS-cog** score reflects **better cognitive function**.
  - Dementia-related behaviors were assessed with the **Neuropsychiatry Inventory[6] (NPI)**, an information-based questionnaire. Derived by multiplying frequency X severity scores, a **lower NPI** summary **score** reflects **fewer/less severe dementia-related symptoms**.
- The behavioral data were analyzed with a repeated measures analysis of variance (ANOVA), with time as the within-subject factor and group as the between-subject factor.
- Neuroimaging outcome measures were assessed at **baseline** and **12-weeks** on a Siemens 3 Tesla Trio Scanner.
- **Arterial spin-labeled (ASL) perfusion MRI**[7] (see schematic below) was used to quantify **cerebral blood flow (CBF)**.

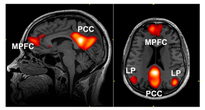


- Anatomical regions of interest (ROIs), generated using FreeSurfer version 5.1, were used to analyze the CBF data.
  - The **superior frontal**, **superior parietal,** and **supramarginal** parcels corresponded to brain regions targeted by the Vielight Neuro Gamma's transcranial LEDs (Light-Emitting Diodes, see below).
  - CBF from the precentral parcel (i.e., primary motor cortex) was used as a control region in the analysis.
  - A repeated measures multivariate analysis of variance (MANOVA) was used to analyze the CBF data, with time and ROI as within-subject factors and group as the between-subject factor.



Approximate position of the Vielight Neuro Gamma transcranial LEDs relative to the FreeSurfer ROIs used in analysis of ASL perfusion data.

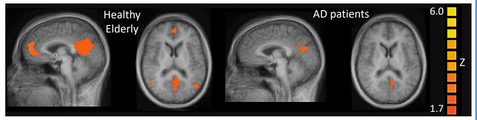
- **Resting state functional MRI** was used to assess **functional connectivity** (i.e., the temporal correlation between spatially distinct brain regions) in the **Default Mode Network (DMN).**
- The DMN is an interconnected group of brain structures that show higher levels of activity when we are awake but not engaged in any specific mental task and lower levels of activity when we are engaged a specific task (e.g., paying attention).[8]



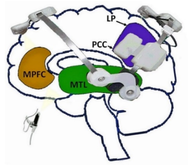
Nodes of DMN:
- Precuneus/Posterior Cingulate Cortex (PCC)
- Medial Prefrontal Cortex (MPFC)
- Lateral Parietal Cortex (LP)

not shown: medial temporal/hippocampus

- There is evidence that the DMN is dysregulated in Alzheimer's disease (AD).[9]

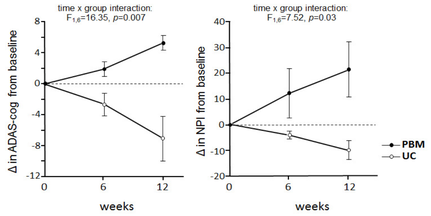


- This is why the LEDs of the Vielight Neuro Gamma device were designed to target nodes of the DMN:

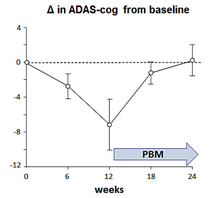


Behavioral Results

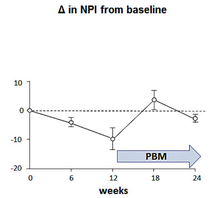
- ADAS-cog and NPI scores improved in the PBM group, but declined in the UC group, after 12 weeks (positive change from baseline = improvement in figure below).



- There was a trend towards improvement on the ADAS-cog in 3 UC participants who chose to undergo 12 weeks of PBM after completing 12 weeks of Usual Care.



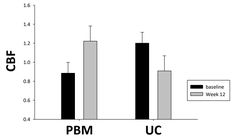
paired *t*-tests:
0 vs. 12 wks: t=1.66, p=0.22
12 vs. 24 wks: t=3.74, p=0.07
0 vs. 24 wks: t=0.61, p=0.61



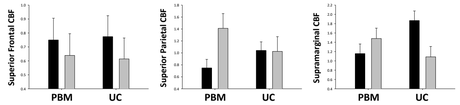
paired *t*-tests:
0 vs. 12 wks: t=2.90, p=0.10
12 vs. 24 wks: t=2.56, p=0.13
0 vs. 24 wks: t=0.38, p=0.74

Imaging Results

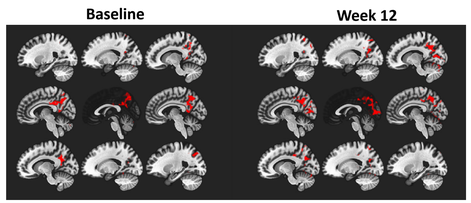
- After 12 weeks, there was greater CBF in the PBM group compared to the UC group (group x time interaction: $F_{1,6}$= 8.46, p<0.03).



- The greatest change in CBF occurred in the parietal lobe in the PBM group (ROI x group x time interaction: $F_{1,6}$= 8.93, p=0.02).

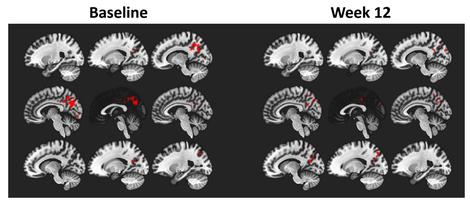


- After 12 weeks, there was greater connectivity in the DMN in the PBM group.



DMN connectivity (to a PCC seed) at baseline vs. Week 12 in the PBM group

- In contrast, there was decreased connectivity in the DMN in the UC group after 12 weeks.



DMN connectivity (to a PCC seed) at baseline vs. Week 12 in the UC group

Connectivity between a seed in the PCC and Lateral Parietal (LP) nodes of the DMN by group and time

	PBM Group				UC Group			
	Baseline		12-weeks		Baseline		12-weeks	
	T(3)	P_{unc}	T(3)	P_{unc}	T(3)	P_{unc}	T(3)	P_{unc}
LLP	4.25	0.02	14.15	<0.001	6.88	0.006	3.89	0.03
RLP	3.98	0.03	11.17	0.002	8.34	0.004	5.04	0.02

CONCLUSIONS

- These behavioral results reaffirm Saltmarche et al.[3] findings that transcranial and intranasal PBM benefits cognitive function in patients with dementia.
- The preliminary findings of increased CBF and DMN functional connectivity support the potential of PBM as a safe, non-pharmacological intervention that can be used to treat patients with dementia in their homes.
- These results suggest that future, larger controlled trials of home PBM treatments for dementia are warranted.

References

1. Hamblin MR (2016) *BBA Clin*. 6:113-24.
2. Tedford CD et al. (2015) *Lasers Surg Med*. 47(4):312-22.
3. Saltmarche AE et al. (2017) *Photomed Laser Surg*. 35(8):432-41.
4. Folstein MF, Folstein SE, McHugh PR (1975) *J Psychiatr Res*. 12:189-98.
5. Rosen WG, et al. (1984) *Am J Psychiatry*. 141:1356-64.
6. Cummings JL (1997) *Neurology*. 48:S10-16.
7. Detre JA, Alsop DC (1999) *Eur J Radiol*. 30:115-24.
8. Greicius MD et al. (2003) *PNAS* 100:253-58.
9. Koch et al. (2012) *Neurobiol Aging*. 33(3):466-78.