Effect of trans-cranial near infrared light 1068 nm upon age-related memory status: a pilot study.

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Abstract

Background We present a pilot study of the Cerebrolite technology, where we explored the effect of multi-modality photo-biomodulation (PBM) therapy, with a peak wavelength of 1068 nm, upon motor function, memory and processing speed reversal in aged individuals who have been diagnosed with mild cognitive impairment (MCI) .**Methods** PBM therapy was performed at home, adopting the Cerebrolite Trans-cranial phototherapy device, an air-cooled light emitting diode LED pulse mounted inside the helmet, with a peak wavelength of 1068 nm, used for 6 min twice daily on age-matched middle-aged subjects. The FDA-approved computerised assessment tool ANAM was adopted to quantify a series of cognitive and motor activities in the treated groups.**Results** A significant improvement in motor function, memory and processing speed was observed in MCI aged individuals with PBM- compared to placebo-treated group. No adverse effects were reported.**Conclusions** PBM therapy may be a promising new non-invasive approach for middle-aged individuals with MCI.

Background

Phototherapy, also known as photobiomodulation (PBM), refers to the use of non-thermal, non-invasive light to achieve a therapeutic outcome, and can apply to a variety of light-emitting devices of various wavelengths. It is the use of a low energy light source to elicit biological effects, also commonly referred to as Low-Level Light Therapy, LLLT, or Low-Intensity Light Therapy, LILT. Interest in recent advances in the use of light emitting diodes (LEDs) has led to their clinical application for a variety of medical and cosmetic uses [1]. Three distinct wavelength stretches of light, including blue (415nm), red (633nm), and near-infrared (830nm, 1060-80nm), have demonstrated efficacy or multiple therapeutic applications, [2]. A previous laboratory research study [3] has shown that human lymphocytes pre-irradiated with 1072 nm light are resistant against subsequent ultraviolet light toxicity. This was the optimal wavelength for cytoprotection in this study . Further studies have shown that this wavelength demonstrated a non-invasive beneficial effect, on spatial memory performance in a mouse model of premature ageing [4]. Furthermore, this wavelength was shown to elicit a range of positive effects upon cellular stress leading to reduced β -amyloid in a mouse model of Alzheimer's disease (AD) [5]. The mechanism of action involves photon absorption in the mitochondria electron-transport chain (cytochrome c oxidase), and up-regulation of selective neuroprotective chaperone genes [5]. A recent pilot double blind, placebo-controlled study provided the first evidence for the utility of the 1060-1080 nm wavelength range in treating age-dependent neurodegenerative diseases. In this study, 28 daily 6-minute exposures (6 active, 3 controls) improved executive functions as measured by clock drawing, praxis memory, visual attention and task switching in patients with dementia [6].

In this present study, we explored, for the first time, the potential for the beneficial effects of 1068 nm upon normal healthy middle-aged individuals.

Cerebrolite Trans-cranial phototherapy device

An air cooled, LED helmet with a peak wavelength of 1068nm was used for 6 minutes twice daily. The peak power of the NIR light output was circa 37 Watts peak optical power achieved by using a unique pulse width modulation. The plan of the device with position of LED panels is shown in Figure 1.

Recruitment

Recruitment was over 3 years, age-matched participants (mean age 57 ± 10 years (Active) and 57 ± 8 years (Placebo) from the general population recruited from Barcelona in Spain and the north of England. The Spanish volunteers were recruited sooner as the local Spanish regulator came to a decision similar to that in the UK, but a year earlier. A total of 27 participants completed the study. Recruitment was facilitated by word of mouth, newspaper advertisements and by posts on social media.

Randomisation

A computer-generated randomisation table was used. The odd numbers were assigned to individuals in the placebo group, and the even numbers were assigned to individuals in the active group.

Assessment tools

FDA-approved computerised assessment test, Automated Neuropsychological Assessment Metrics (ANAM) [7-11].

The ANAM assessment tool identified 16 different modalities: 1. composite score (overall performance), 2. simple reaction time (SRT 1), 3. code substitution (learning), 4. procedural reaction time, 5. mathematical processing (working memory 1), 6. matching to sample (spatial working memory), 7. code substitution- delayed (delayed memory), 8. simple reaction time (SRT 2), 9. Go/no-go (inhibition), 10. logical relations (reasoning), 11. spatial processing, 12. tower puzzle (problem solving), 13. tapping R hand (motor speed), 14. tapping L hand (motor speed), 15. 2-choice reaction time (attention/processing speed), 16. running memory (working memory 2).

Methods

Interested participants were either directed to the trial website (www.cerebrolite.com) or given a participant information sheet to read prior to their first interview with an assessor. All assessors held a registered qualification, to ensure compliance with protocol. Each participant was given the opportunity to ask questions and seek clarity regarding the requirements of the study before participation. Participants signed a consent form, a loan agreement, and provided base line data on their medication and general health. The participants were then assigned to an intervention according to a computer generated randomisation table to receive either an active or placebo device. Each participant was then assessed on 3 separate days, to minimise the impact on the results by day to day variations in cognitive performance as a positive outcome was likely to be small, but measurable.

The participants were then shown a Cerebrolite device and given the appropriate instructions on how to use the device and the participants were requested to use the Cerebrolite for at least 28 days. They were reassessed between 3 and 28 days later on 3 separate days. Some participants were only available over a period of a few weeks for re-assessment, and, therefore, the interval between test assessments was variable between individuals. The Cerebrolite was used twice daily until the last assessment was concluded.

Results

Thirty five participants were recruited and were assessed using the ANAM assessment tool, where $n=27$ completed the tasks and took part in follow-up (14 active and 13 placebo participants). Five of participants opted out because they found the assessments too challenging and three participants changed their mind. Due to participant time constraints 7 of the participants did not have 3 post treatment assessments, but only had 2 post-treatment assessment (4 in the active group and 3 in the placebo group).

In the active group there were 11 right-handed and 3 left-handed individuals and in the placebo group there were 11 right-handed and 2 left-handed individuals.

When comparing pre-treatment to post-treatment assessment scores and comparing the active to the placebo groups the following four selected modalities of the ANAM test achieved statistical significant improvement:

1. Composite score (measurement of overall performance)
2. Mathematical processing (working memory)
3. Code substitution – delayed (delayed memory)
4. Tapping- Right hand (motor speed R hand)

Processing speed in the placebo group demonstrated deterioration in performance compared to base line. In the placebo group, the comparison to base line did not yield any significant improvement. Further analysis involved the subtraction of the baseline scores from the post-treatment scores in both the active and placebo group, and comparison of the results between active and placebo arms of the study.

Statistical evaluation

For each participant and each modality, pre- and post-treatment, the mean of all source data was calculated. These basic mean values formed the data units for the analysis. Tables 1A and 1B contain statistical summaries for the ANAM sixteen modalities. A positive value shows improvement. Pre- and post-treatment mean values across participants are shown for the active and placebo groups. The main focus of the analysis is on the changes in basic mean scores, relative to pre-treatment. The Tables 1 and 2 show mean changes across participants and corresponding p-values from paired-comparison t-tests. Also shown are counts of participants with results better after treatment and those with results worse

after treatment. The sign test was applied to these counts and the resulting p-values are shown. The tables also show p-values from two-sample t-tests and Wilcoxon rank-sum tests, comparing changes in basic mean scores between the active and the placebo groups.

	Composite score	Simple Reaction Time 1	Learning	Maths Process Speed	Work memory	Spatial memory	Delayed memory	Simple Reaction Time 2
Active								
Mean pre-Tx*	0.22	0.060	0.67	-0.61	0.27	0.30	-0.187	0.27
Mean post-Tx	0.72	0.22	0.98	0.086	0.84	0.55	0.48	0.14
Mean change	0.50	0.16	0.31	0.70	0.57	0.25	0.67	-0.13
p (t-test)	0.00053	0.28	0.076	0.013	0.0042	0.11	0.000084	0.31
Number > 0	13	9	10	11	12	10	13	5
Number< 0	1	5	4	3	2	4	1	9
p (sign test)	0.0018	0.42	0.18	0.057	0.013	0.18	0.0018	0.42
Placebo								
Mean pre-Tx	-0.51	-0.16	0.45	-0.39	0.37	0.045	0.14	0.33
Mean post-Tx	-0.47	-0.21	0.66	-0.14	0.41	-0.2	0.35	0.36
Mean change	0.04	-0.047	0.21	0.25	0.03	-0.26	0.21	0.037
p (t-test)	0.79	0.61	0.28	0.20	0.82	0.27	0.13	0.90
Number > 0	8	7	8	6	7	5	8	6
Number< 0	5	6	5	7	6	8	5	7
p (sign test)	0.58	1.0	0.58	1.0	1.0	.58	.58	1.0
Active vs Placebo								
p (t-test)	0.020	0.23	0.67	0.15	0.039	0.069	0.015	0.58
p (Wilcoxon)	0.012	0.33	0.59	0.19	0.020	0.11	0.020	0.48

Table 1A. Comparison between the pre-treatment and post treatment scores together with a comparison between the active and placebo groups for the first 8 components of the ANAM assessment tool (modalities 1-8). * pre-treatment

	Inhibition	Reasoning	Spatial process	Problem solve	Motor speed R	Motor speed L	Attention Process speed	Working memory 2
<u>Active</u>								
Mean pre-Tx*	0.11	0.57	0.26	0.38	-0.046	0.10	0.35	0.30
Mean post-Tx	0.16	0.71	0.19	0.54	0.57	0.38	0.34	0.57

Mean change	0.052	0.14	-0.069	0.16	0.61	0.28	-0.010	0.27
p (t-test)	0.76	0.35	0.70	0.34	0.010	0.052	0.92	0.039
Number > 0	8	8	9	10	11	9	8	11
Number< 0	6	6	5	4	2	5	6	3
p (sign test)	0.79	0.79	0.42	0.18	0.022	0.42	0.79	0.092
<u>Placebo</u>								
Mean pre-Tx	0.41	0.42	0.35	0.25	0.46	0.24	0.68	0.24
Mean post-Tx	0.35	0.35	0.15	0.15	0.53	0.28	0.32	0.17

Mean change	-0.065	-0.07	-0.20	-0.092	0.063	0.034	-0.36	-0.068
p (t-test)	0.75	0.67	0.33	0.57	0.64	0.86	0.028	0.66
Number > 0	7	6	5	6	9	9	2	8
Number< 0	6	7	8	7	3	4	11	5
p (sign test)	1.0	1.0	0.58	1.0	0.092	0.27	0.022	0.58
<u>Active vs Placebo</u>								
p (t-test)	0.66	0.34	0.62	0.27	0.034	0.29	0.054	0.088
p (Wilcoxon)	0.54	0.47	0.81	0.21	0.021	0.17	0.033	0.29

Table 1B. Comparison between the pre-treatment and post treatment scores together with a comparison between the active and placebo groups for the second 8 components of the ANAM assessment tool (modalities 9-16). * pre-treatment

Discussion

Anecdotal experience has identified the Cerebrolite technology has a positive effect upon motor function, memory and processing speed. The improvement in motor function was profoundly noted in individuals with Parkinson's disease. This present pilot study has supported the anecdotal experience with statistical significance. These results suggest that transcranial LED stimulation with Cerebrolite technology improves examples of motor function, as well as working and delayed memory performance, and may have potential for treating or preventing deficits resulting from neuropsychological disorders or normal healthy ageing [11].

This present study concurs with recent studies [12] which reported that transcranial laser stimulation with 1064nm, localised to prefrontal cortex, enhanced sustained attention and short-term memory in young adult humans (undergraduate students, mean age 20), which was extended, recently, to show enhanced executive function; transcranial laser stimulation enhanced performance in the Wisconsin Card Sorting Task (gold-standard of executive function), compromised in normal ageing and a number of neuropsychological disorders [13]. Furthermore, in another study, AD participants who received 1068 nm LED treatment, made fewer errors and showed improved set-shifting ability, changes in executive functioning; clock drawing, immediate recall, praxis memory, visual attention and task switching, relative to placebo controls, as well as a trend to improved EEG amplitude and connectivity measures [6].

A review of the initial scores of the active and placebo groups indicated the groups were not balanced, which may have impacted upon the outcome measures. A further study with balanced groups is required.

Conclusions

Overall, this present study provides further evidence supporting the beneficial effects of 1068 nm PBM upon ageing and age-related brain dysfunctions, worthy of further exploration in larger cohort balanced group studies.

List Of Abbreviations

PBM photo-biomodulation

MCI mild cognitive impairment

LED light emitting diode

FDA US, Food and Drug Administration

NIR near infrared

LILT low intensity light therapy

AD Alzheimer's disease

NHS UK, National Health Service

REC research ethics committee

HRA UK, Health Research Authority

ANAM Automated Neuropsychological Assessment Metrics

Declarations

Ethics approval and consent to participate

The study design was submitted to the North East - York Research Ethics Committee, REC reference: 16/NE/300. The Ethical decision was reached on October 21, 2016. The Committee stated that the study did not require ethical review by an NHS REC for the following reasons: a) The study does not involve the use of a medical device for treatment or assessment of a medical condition; b) The study involves only healthy volunteers; c) The study does not involve NHS patients. "Furthermore, after discussion with the HRA, we assessed that the project did not require HRA Approval, as healthy volunteers, were consented and seen at private non-NHS premises." The HRA stated "we are of the view that the project would more appropriately be classified and managed as service evaluation, rather than research intervention".

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable; there is no participant identifiable information in the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

G Dougal is a majority shareholder in Maculume Ltd

Funding

Maculume Ltd provided the funding for the study.

Author's contributions

G Dougal, responsible for the supervision, study design and manuscript composition of the study.

PL Chazot and A Ennaceur, both equally responsible for study design and manuscript composition and editing of the study.

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Figures

Figure 1

The Cerebrolite technology helmet showing positions of the LED units. A) Front view and B) Side view