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Can transcranial brain-targeted bright light treatment via ear canals be effective in relieving symptoms in seasonal affective disorder? – A pilot study ☆

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ABSTRACT

Bright light therapy (BLT) is widely accepted as first-line treatment of seasonal affective disorder (SAD). However, the mechanism of action of BLT is still widely unknown. On the other hand, in mammals, light penetrates the skull bone and reaches the brain, and extra ocular transcranial phototransduction has physiological influences such as changed reproductive cycles and increased brain serotonin levels. Therefore, we challenged the existing conceptual framework that light therapy would only be mediated through the eyes. Consequently, we run a pilot study on the putative effect of transcranial bright light in the treatment of SAD. The light was produced using light-emitting diodes (LEDs), which were attached to earplugs. The amount of photic energy was 6.0–8.5 lumens in both ear canals, and the length of treatment was 8 or 12 min five times a week during a four-week study period. Subjects were recruited through advertisements in the city of Oulu, Finland (latitude 65°01′N) during 14 January 2009–03 February 2009. The final patient series consisted of 13 (aged 37.1 ± 7.2 years) physically healthy indoor workers suffering from SAD according to DSM-IV-TR criteria. Severity of depressive symptoms was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) and Beck Depression Inventory (BDI)-21. Furthermore, severity of anxiety symptoms was measured by the 14-item Hamilton Anxiety Rating Scale (HAMA). The HAMD-17 mean sum score at screening was 23.1 ± 1.6. Ten out of 13 SAD patients (76.9%) achieved full remission (i.e., HAMD-17 sum score $\leqslant$7), and 92.3% (12/13) at least 50% reduction in HAMD-17 sum scores at "Week 4". By using a mixed regression model of repeated measures (AR-1) controlling for age, gender, and HAMD-17 mean sum score at screening, significant differences were found comparing the HAMD-17 mean sum scores of "Week 0" with the corresponding scores at the "Week 3" ($t = -2.05$, $p = 0.045$) and "Week 4" visit ($t = -2.77$, $p = 0.008$). Correspondingly, significant differences were found comparing the BDI-21 mean sum scores (15.2 ± 6.7) of "Week 0" with the corresponding scores at the "Week 3" ($t = -2.37$, $p = 0.021$) and "Week 4" visit ($t = -3.65$, $p < 0.001$). The HAMA mean sum score at screening was 20.5 ± 5.4. During the study period, 12 out of 13 (92.3%) patients achieved at least 50% reduction in their HAMA sum scores, and in 10 out of 13 patients (76.9%), the HAMA sum score was <7. In conclusion, it is hard to believe that our findings could be explained solely by placebo effect. Consequently, the basic assumptions underlying extraocular photoreception in humans deserve to be reconsidered. Given that a proper placebo treatment can be implemented via ear canals, further investigations with randomized placebo-controlled and/or dose-finding study designs regarding the extraocular transcranial bright light in the treatment of SAD are called for.

Introduction

The seasonal pattern of recurrent episodes of depression, either unipolar or bipolar, has become known as seasonal affective disorder (SAD) [1–3]. The precise pathogenesis of SAD is still elusive

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despite several explanatory theories [2,4]. Both DSM-IV and ICD-10 are open with regard to the season during which a major depressive episode recurs [1–3,5], although ICD-10 has only provisional diagnostic criteria for SAD [5]. Since winter SAD is far more prevalent than summer SAD, the term SAD usually refers to winter SAD [3]. It has been estimated that the prevalence of SAD is around 1.2% in general populations, but the prevalence figures differ a lot due to methodological differences in epidemiological studies [3].

Although evidence has not been fully confirmed [6], bright light therapy (BLT) is widely accepted as first-line treatment of SAD in guidelines of high repute [7–9]. In a systematic review and meta-analysis, the effect size for the reduction of depressive symptoms by BLT (eight randomized control trials (RCTs)) in the treatment of SAD was 0.84 (95% CI 0.60–1.08) [10]. However, there was significant heterogeneity among the studies. Correspondingly, the guideline of the National Institute for Health and Clinical Excellence (NICE) found that when compared with waiting list controls, bright light reduced depressive symptoms significantly [6]. However, the guideline concludes that it is unclear whether this effect is greater than placebo effect [6]. In addition, a statistically significant reduction of depressive symptoms has been found in the treatment of SAD by using dawn simulation [11], with an effect size (five RCTs) of 0.73 (0.37–1.08) in a meta-analysis [10]. However, the corresponding evidence has been questioned [6].

The hypothesis

The mechanism of action of BLT and dawn simulation in the treatment of SAD is still widely unknown [7,11]. On the other hand, there is evidence that in mammals, (a) significant amount of light penetrates the skull bone and reaches the brain, and (b) extra ocular transcranial phototransduction has certain physiological influences such as changed reproductive cycles and increased brain serotonin levels (cf. Campbell et al. 2001) [12]. Therefore, we have challenged the existing conceptual framework concerning the mechanisms of action of bright light: of note is the relatively weak initial evidence concerning the paradigm that light therapy would only be mediated through the eyes [13].

Opsins are known to mediate phototransduction in both visual and non-visual systems by being transmembrane proteins acting as G-protein-coupled receptors (GPCRs) [14]. Per se, all known vertebrate photoreceptors use an opsin protein bound to a vitamin A-chromophore as photopigment. Over species and opsins, the principle of phototransduction is always the same: when the photon is absorbed by the retinal chromophore, this molecule isomerizes from 11-*cis*-retinal form to the all-*trans*-retinal form. This conformational change allows opsin proteins intracellular terminus to trigger a G-protein cascade leading into rise in receptor membrane potential. The cascade converting photic energy into neural responses is called phototransduction [14–16].

Until now, several studies, per se, show genes of extravisual opsins expressed also in mammalian brain in mRNA-level [17–24]. Furthermore, there is now initial evidence that, e.g., encephalopsin, also called as OPN3 or panopsin [19] exists in protein level in human brain [25,26]. OPN3 has been suggested to play a role in non-visual photic processes such as the entrainment of circadian rhythm or the regulation of pineal melatonin production [23,24] even though the exact function of encephalopsin has remained largely unknown. However, the role of OPN3 is most likely related into it's phylogenetic background as an extraretinal ciliary phototransductive membrane protein [16]. Indeed, opsin-proteins' capability to adopt their functional phototransductive role when expressed on extra-visual neurons is shown in studies, where foreign species' opsin-genes are added to neurons via viral vectors [27–29]. In these studies, opsin mediated phototransduction has been confirmed by electrical intracellular recordings during illumination [28,29]. From that point of view, it is reasonable to hypothesize, that also endogenous opsins will carry their functional role as a part of extravisual phototransduction. Consequently, it is reasonable to hypothesize that light therapy would not solely be mediated through the eyes.

We were encouraged to hypothesize that extraocular light would be helpful in subjects with SAD. Consequently, we run a pilot prospective uncontrolled study on the putative effect of transcranial bright light in the reduction of depressive symptoms in patients suffering from winter SAD.

Evaluation of the hypothesis

Description of the bright light device

We developed a non-invasive photon application device, a VALKEE bright light device (Valkee Ltd., Oulunsalo Finland), which was approved as a medical device in the European Union on 30 March 2010. It was specially designed to target bright light treatment transcranially towards the brain via ear canals. The light was produced by using light-emitting diodes (LEDs), which were attached to earplugs. The light intensity at the end of both light guides in the ear canals was 6.0–8.5 lumens (lm) during this pilot study. Initially, the length of the light treatment was 8 min, and if 8 min was tolerable but remission was not achieved after 2 weeks, the length of the treatment was increased to 12 min. A trained study assistant ensured that the bright light device was used properly.

Case definitions

Subjects suffering from seasonal depressive symptoms were recruited through advertisements and pre-screened by phone by a psychiatrist in the city of Oulu, Finland (latitude 65°01′N). During 14 January 2009–03 February 2009, after consenting in writing, all subjects were interviewed at "screening visit" by an experienced 17-item Hamilton Depression Rating Scale (HAMD-17) [30] educated psychiatrist (A.L. or M.T.). The final patient series consisted of physically healthy employed indoor workers ($n = 13$; 4 males, 9 females, aged 18–45 years). The ethical committee of Oulu University Hospital approved the study protocol.

Diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1] for recurrent major depression (moderate or severe) was obtained using the Mini International Neuropsychiatric Interview (MINI) [31]. In addition, patients had to fulfill the diagnostic criteria for SAD according to DSM-IV [1]. The severity of depressive symptoms was assessed by using the HAMD-17 [30], and only those with HAMD-17 sum score $\geqslant 22$ at "screening visit" were included in the present study. The exclusion criteria were as follows: lifetime psychotic disorders, bipolar disorders, severe personality disorders, substance abuse or dependence, lifetime suicide attempt or suicidal ideation during the past month [32], any psychotropic medications, and other bright-light therapy for the current SAD episode. Pregnant females were also excluded.

Study protocol

In order to ascertain the severity of depressive symptoms and to decrease the possibility of including potential placebo responders, HAMD-17 was repeated after 1 week (7 days ± 1 day) after the "screening visit" at the "Week 0" visit. Transcranial brain-targeted bright light treatment via ear canals was started within one day after the "Week 0" visit. During the four-week study period, the patients received bright light treatment five times a week at Oulu Deaconess Institute. However, due to patient-related reasons, one non-attendance per week was allowed. HAMD-17 was conducted

weekly during the study period, and also 1 week (at "Week 5" visit) after the end of the study period. Furthermore, severity of anxiety symptoms was measured by the 14-item Hamilton Anxiety Rating Scale (HAMA) [33] weekly from the "Week 0" visit throughout the study. To assess the patients' subjective view of their depressive symptoms, self-rated Beck Depression Inventory (BDI)-21 [34] was assessed weekly from the "Week 0" visit throughout the study. The patients did not receive any other treatments during the study period.

Statistical analyses

The means of the HAMD-17 sum scores as well as BDI-21 sum scores at five time points (Week 0, Week 1, Week 2, Week 3, and Week 4 as well as post-treatment visit [Week 5]) were compared using mixed regression model of repeated measures, with autoregressive AR-1 covariance structures. Age and gender were included as potential covariates, as was the HAMD-17 sum score at screening visit on HAMD-17 analyses. The statistical analyses were performed with SAS software package, version 9.2.

Empirical data

The mean age of the patients with SAD was 37.1 ± 7.2 years. The median number of earlier SAD-periods was 5 (range 2–20), and none of the patients had previously had non-seasonal depressive episodes; one of the patients had a comorbid social phobia. The mean duration of the current SAD episode was 11.2 ± 3.4 weeks. The patients with SAD had neither any significant physical disorders nor any concurrent medications.

The HAMD-17 sum score at the screening visit was 23.1 ± 1.6. Of the patients with SAD, 76.9% (10 out of 13 patients) achieved full remission (i.e., HAMD-17 sum score $\leqslant 7$) until the "Week 4" visit. When compared with the "Week 0" visit, only one patient did not achieve at least 50% reduction in HAMD-17 sum scores until the "Week 4" visit. Statistically significant differences were found when comparing the HAMD-17 mean sum scores of "Week 0" with the corresponding scores at the "Week 3" ($t = -2.05$, $p = 0.045$) and "Week 4" visit ($t = -2.77$, $p = 0.008$) (Fig. 1).

Regarding self-reported depressive symptoms, the BDI-21 mean sum score at the "Week 0" visit was 15.2 ± 6.7. Significant differences were found when comparing the BDI-21 mean sum scores of "Week 0" with the corresponding scores at the "Week 3" ($t = -2.37$, $p = 0.021$) and "Week 4" visit ($t = -3.65$, $p < 0.001$) (Fig. 1). Of note is that until "Week 4" visit, the BDI-21 sum score was 7 or less in 12 out of 13 patients; Furthermore, when compared with the "Week 0" visit, all of these 12 patients achieved at least 50% reduction in their BDI-21 sum scores.

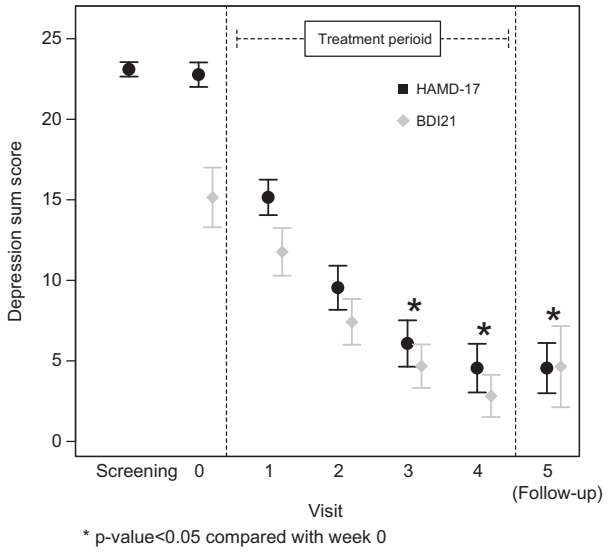

Fig. 1. 17-Item Hamilton Depression Rating Scale (HAMD-17) and Beck Depression Inventory (BDI-21) sum scores in subjects treated by transcranial brain-targeted bright light via ear canals. Data expressed as mean ± SEM.

With regard to anxiety symptoms, the HAMA mean sum score at screening was 20.5 ± 5.4. During the study period, 12 out of 13 (92.3%) patients achieved at least 50% reduction in their HAMA sum scores, and in 10 out of 13 patients (76.9%), the HAMA sum score was <7.

Consequences of the hypothesis and discussion

We have challenged the existing conceptual framework concerning the mechanisms of action of bright light in the treatment of SAD, i.e., that light therapy would only be mediated through the eyes [13]. For example, OPN3 [19,20], while existing in protein level in human brain [25,26] might play a role in non-visual phototransduction. We have initiated our human brain opsin research branch by showing that OPN3 exists in several different brain areas outside the visual pathway [26]. Furthermore, there exist several other human opsins which might have a role in non-visual phototransduction given that over 1000 different opsin sequences are known in animal kingdom [16]. In addition the effect on non-visual light can potentially be mediated through non-opsin mediated pathways [35,36].

To test our hypothesis that extraocular light would be helpful in subjects with SAD we run a pilot prospective uncontrolled study on the putative effect of transcranial bright light in patients suffering from winter SAD. Our preliminary finding was that both self-reported and psychiatrist-rated depressive symptoms decreased significantly during the 4-week study period.

Despite the fact that our finding is novel and interesting, our results need to be discussed critically with caution. We are fully aware of the possible placebo effect due to, e.g., regular bright light treatment sessions and monitoring of depressive symptoms in this patient series [6,37]. However, we think that it is unlike that a potential placebo effect only would explain the comparably [11,37,38] high remission and response rates in our pilot study. Therefore, in our opinion, our preliminary results are so important that they challenge the existing conceptual framework concerning the mechanisms of action of bright light: in this context, we would like to emphasize the relatively weak initial evidence concerning the paradigm that light therapy would solely be mediated through the eyes [13]. The light in the pioneer work of Wehr and colleagues (1987) consisted of 2500 lux of full-spectrum light exposed from a distance of three feet from the patients to their "eyes but not their skin", or vice versa [13]. Of note is, however, that natural bright sunlight at noon (about 100,000 lux) [39] far exceeds the amount which is normally emitted by conventional bright light devices (2500–10,000 lux). Thus, in our opinion, the relatively low illuminations derived from conventional light devices reach deep structures of the brain mainly visually, but only to some extent by penetrating via other routes. The strength of this study and our novel application is that we were able to transmit a photic energy far exceeding the amount which is normally visibly tolerable and emitted by conventional BLT devices.

Our study method also has some other limitations than those already acknowledged above. In this pilot phase, we did not have a control group. Secondly, we are aware that the regular amount of daylight increases towards the spring. However, the study was conducted during the darkest season of the year in the city of Oulu (latitude 65°01′N), which is located only about 170 km south of the

Arctic Circle. In Northern Finland, the amount of daylight during winter (December–February) is only about 1/8 of that during the spring (March–May) [40]. In addition, all patients were indoor workers who hardly saw the sun during daylight hours. Thirdly, we did not analyse the atypical symptoms of SAD by the Seasonal Affective Disorders version of the Hamilton Depression Rating Scale (SIGH-SAD) [41]; however, due to relatively strict HAMD-17 criteria (sum score $\geqslant$22) and the structured use of the DSM-IV criteria for MDD and "seasonal pattern", we think that the SAD diagnoses of the study subjects were valid.

In conclusion, our novel findings point out that the putative role of the extraocular transcranial route of light transmission into the brain is worth researching in the treatment of SAD. Besides showing both the existence and functional role of non-visual opsins in human brains, also further investigations with randomized placebo-controlled and/or dose-finding study designs assessing the intensity and time of the extraocular transcranial bright light in the treatment of SAD are called for. The most fascinating eventual aim would be to show the ultimate mechanism of action of bright light in relieving the symptoms of SAD. If endogenous human brain opsins turn out to have a role in the extravisual phototransduction, and extraocular transcranial route of light transmission into brain effective in the treatment of SAD, it would bring additional support to recognize SAD as an independent entity as suggested earlier [42].

Role of the funding source

This study was partly funded by Oulu Deaconess Institute and Valkee Ltd.

Conflict of interest statement

MT is a minor shareholder in Valkee Ltd., was reimbursed by Pfizer for attending one conference, was paid by Pfizer, BMS, Eli Lilly, Servier and Astra Zeneca for speaking on different educational occasions, and has received advisory panel payments from Pfizer and H. Lundbeck A/S for three meetings. JN is a shareholder and CSO of VALKEE Ltd. company (Oulu, Finland), which is a producer and developer of the bright light devices for SAD. MSc. AL and JJ report no financial relationships with commercial interests. HJ is a research coordinator in Valkee Ltd. AA is a shareholdrer and CTO of Valkee Ltd. PR was paid by Astra Zeneca and Eli Lilly for speaking on different educational occasions, and has received advisory panel payments from Novartis Finland. TT is a minor shareholder in Valkee Ltd.

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