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HumanCharger - Summary of published, peer-reviewed findings

1. Transcranial light alters melanopsin and monoamine production in mouse (*Mus musculus*) brain

Authors: Flyktman A, Jernfors T, Mänttäri S, Nissilä J, Timonen M, Saarela S
Journal: J Neurol Res. 2017;7(3):39-45
Summary: Light is the main signal that entrains the mammalian circadian system. One of the key molecules transmitting light information and entraining the circadian clock is melanopsin (OPN4). Thirty visually blind adult (8-10 weeks old at the beginning of the study) male mice were used in this study. The mice were randomly assigned to three different groups: control, morning-light group and evening-light group. Transcranial light was given under anesthesia via ear canals for 4 weeks, five times a week, 8 minutes per mouse. The control group was anesthetized and headphones were inserted, but no light was given. The results of this study show that transcranial light has a significant effect on OPN4 expression in the mouse brain. The amount of OPN4 increased significantly in transcranially illuminated mice when compared to controls. This study also shows that serotonin concentration in the cortex is affected by light illumination. Results are able to show the connection between transcranial light and circadian rhythmicity, since the results of the expression level of OPN4 in the cerebellum differed between the test groups. Based on the findings of this study, light-activated molecules of the brain can be stimulated with transcranial light.

2. The distribution of melanopsin (OPN4) protein in the human brain

Authors: Nissilä JS, Mänttäri SK, Särkioja TT, Tuominen HJ, Takala TE, Kiviniemi VJ, Sormunen RT, Saarela SYO, Timonen MJ
Journal: Chronobiology International, 2017;34(1):37-44
Summary: This is the first study to show that melanopsin (OPN4) exist at protein level outside the retinohypothalamic tract (RHT) in human brain. Main finding of this study is that OPN4 is actually widely distributed in human brain given that it was expressed, in general, in all investigated 18 brain areas, including those with importance to the regulation of essential body functions and also new evolved part like neocortex. These results are in line with the earlier findings of Allen Institute for Brain Science showing widely distributed OPN4 gene activity in human brain (Hawrylycz et al.2012). Western blotting and immunohistochemistry, as well as immunoelectron microscopy, were used to analyze the existence and distribution of OPN4 protein in 18 investigated areas of the human brain in samples obtained in forensic autopsies from 10 male subjects. The wide distribution of OPN4 in central areas of the human brain evokes a question whether ambient light has important straight targets in the human brain outside the RHT.

3. Human brain reacts to transcranial extraocular light

Authors: Sun L, Peräkylä J, Kovalainen A, Ogawa K H, Karhunen P J, Hartikainen K M.
Journal: PLOSONE, 2016, 24: 11 (2): e0149525
Summary: This study demonstrates that extraocular light affects human brain functioning. Extraocular light modulated attention-related brain responses, specifically related to emotion-attention interaction. Study confirms that light is capable of penetrating the human skull via ear canals and reach the temporal lobe of the brain. Because the brain is floating in cerebrospinal fluid, transmitted light might be widely dispersed, thus illuminating the basal surface of temporal lobe. Penetration of light through ear canals was investigated on a human cadaver after the brain was removed upon autopsy. Light penetration of the skull was visible when viewed both in lighted and dark conditions. Light was able to reach intracranial space through the ear canals and was visible at the base of the skull under the temporal lobes.

4. Transcranial bright light and symptoms of jet lag: a randomized, placebo-controlled trial

Authors: Jurvelin H, Jokelainen J, Takala T.
Journal: Aerospace Medicine and Human Performance, 2015;86(4):344-350.
Summary: This randomized, double-blind, placebo-controlled field study demonstrates that intermittent transcranial bright light exposure via ear canals alleviates jet lag symptoms. A total 55 healthy male subjects completed the study. Subjects were required to travel by plane from Finland (time zone: +2) to North America (time zone: -5 to -8) and stay a minimum of 1 week in their destination time zone. During the post-travel period, subjects were exposed to TBL or placebo treatment four times per day 12 min each at predetermined times. TBL or placebo exposures were administered every 2 h between 08:00 and 14:00 on travel day 0 and every 2h between 10:00 and 16:00 on post-travel days 1-6. The subjects were randomly assigned to the bright light treatment (N=25) group or the placebo (N=30) group. The study set-up for the placebo group was the same except that the bright light device was inactive. The effect of TBL on jet lag symptoms was measured after traveling eastwards. Symptoms of jet lag were measured by the Visual Analog Scale (VAS), the Karolinska Sleepiness Scale (KSS), and the Profile of Mood States (POMS). There were a significant reduction of overall jet lag symptoms, subjective sleepiness, fatigue, inertia and forgetfulness when comparing the TBL group (N=25) to the placebo group (N=30).

5. Transcranial light affects plasma monoamine levels and expression of brain encephalopsin in the mouse

Authors: Flyktman A, Mänttäri S, Nissilä J, Timonen M, Saarela S.
Journal: The Journal of Experimental Biology, 2015; 218:1521-1526
Summary: This study is the first to show that transcranial light has a significant effect on OPN3 expression in the mouse brain. The study also shows that because of transcranial light, dopamine and noradrenaline concentrations increased significantly in the plasma and adrenalin gland. Thirty adult male mice were used in this study. Mice were blind. Transcranial light was given via ear canals for 4 weeks, five times a week. Based on these findings, it is reasonable to hypothesize that light-activated molecules can also be stimulated transcranially, not only through the retina.

6. Effects of bright light treatment on psychomotor speed in athletes.

Authors: Tulppo MP, Jurvelin H, Roivainen E, Nissilä J, Hautala AJ, Kiviniemi AM, Kiviniemi VJ, Takala T.
Journal: Front Physiol. 2014;5:184
Summary: Recent fMRI findings suggested that transcranial bright light (TBL) might have physiological effects on brain functions in humans. The present study investigated if TBL treatment was able to improve psychomotor speed in professional ice hockey players in a randomized, placebo controlled design. A total of 22 pro hockey players (N=11 TBL group; N=11 placebo group; overall mean age ± SD: 25 ±5 yrs) received either 12 min of TBL or placebo every morning between 8 and noon for a period of 24 days. Psychomotor speed using a visual warning signal paradigm was tested before and after trial completion and data were analyzed for mean reaction time and mean motor time. Results showed that psychomotor speed, particular motor time, improved after 24 days of TBL treatment compared to placebo in a group of professional ice hockey players.

7. Transcranial bright light exposure via ear canals does not suppress nocturnal melatonin in healthy adults –a single-blind, sham-controlled, crossover trial.

Authors: Jurvelin H, Takala T, Heberg L, Nissilä J, Rüger M, Leppäluoto J, Saarela S, Vakkuri O.
Journal: Chronobiol Int. 2014; 31(7):855-860
Summary: The present study investigated the effects of transcranial bright light (TBL) on melatonin and cortisol secretion in healthy volunteers. 8 subjects (3F, 5M; mean age ± SD: 27± 5 yrs) were

exposed to TBL during the night-time in a randomized, placebo controlled study design. Subjects reported to the laboratory in the evening (21 h) and were subjected to the same light/dark rhythm in both conditions (16L:8D; lights off at 23 h, lights on at 07 h) prior to the TBL or placebo exposure form 01:10-01:34 h. Saliva and urine samples for melatonin and cortisol were collected at noon, 18, 21, 22, 23, midnight, 01, 02, 03, 06, 07, 08, and 09h. Results clearly showed that neither melatonin or cortisol secretion nor the circadian rhythm of both endocrine markers was affected by the nocturnal exposure to TBL compared to placebo. This is in line with recent findings showing no melatonin suppression due to TBL exposure in the late evening (Bromundt et al., 2013).

8. Altered resting-state activity in seasonal affective disorder.

Authors: Abou Elseoud A, Nissilä J, Liettu A, Remes J, Jokelainen J, Takala T, Aunio A, Starck T, Nikkinen J, Koponen H, Zang YF, TervonenO, Timonen M, Kiviniemi V.

Journal: Hum Brain Mapp. 2014 Jan;35(1):161-72

Summary: Resting state functional brain activity provides a method to detect an existing neurobiological substrate for various disorders, including Seasonal Affective Disorder (SAD). For this purpose, a total of 90 subjects (45 SAD patients; 45 healthy controls) underwent an fMRI to determine functional connectivity of various brain areas in the resting state. A total of 47 resting state networks (RSNs) were investigated. The results showed a clear difference in functional connectivity between SAD patients and healthy, age, gender and ethnicity-matched controls in 11 out of the 47 tested RSNs. The SAD patients showed increased functional connectivity in attentional, visual, and sensomotoric RSNs. These findings support previous findings of psychomotor, attentional, and cognitive impairments seen in SAD patients. Interestingly enough, the same brain areas showed increased activity in healthy controls when exposed to TBL.

9. Transcranial bright light treatment via ear canals in seasonal affective disorder: a randomized controlled double-blind dose-response study

Authors: Jurvelin H, Takala T, Nissilä J, Timonen M, Rüger M, Jokelainen J, Räsänen P

Journal: BMC Psychiatry, 2014; **14**:288

Summary: In a 4 week trial, 89 patients suffering from SAD were randomly assigned to one of three treatment groups and received either a low (1 lumen), medium (4 lumen), or high dose (9 lumen) of daily bright light via ear canals for 12 minutes in the morning. Depressive symptoms and cognitive performance were assessed using standard psychiatric instruments such as the Beck Depression Inventory (BDI) and the Trial Making Test (TMT) at the beginning, during, and at the end of the trial. The results showed a significant, at least 50% reduction of depressive symptoms in 74-79% of the patients according to the BDI in all three treatment groups as well as a significant improvement of cognitive performance compared to baseline.

10. Stimulating brain tissue with bright light alters functional connectivity in brain at the resting state.

Authors: Starck T, Nissilä J, Aunio A, Abou-Elseoud A, Remes J, Nikkinen J, Timonen M, Takala T, Tervonen O, Kiviniemi V.

Journal: World Journal of Neuroscience 2012; 2:81-90

Summary: 50 healthy subjects were randomized into two groups (*N*=24 experimental group, *N*=26 control group) and either received 12 min of transcranial bright light therapy or sham, i.e. no light, while being subjected to Functional Magnetic Resonance Imaging (fMRI). The results of the fMRI showed a clear increase in neural connectivity of the visual cortex and senso-motoric areas of the cortex under the transcranial light compared to the sham group. This suggests the brain to be light perceptive. In addition, these were the same brain areas that showed increased connectivity in the studies by Abou-Elseoud et al. (2011; 2014).

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

Authors: Timonen M, Nissilä J, Liettu A, Jokelainen J, Jurvelin H, Aunio A, Räsänen P, Takala T.

Journal: Med Hypotheses. 2012 Apr;78(4):511-5.

Summary: In this initial pilot study, 13 SAD patients were subjected to a daily dose of 8-12 min of transcranial bright light therapy for 3 weeks. Depressive and anxiety symptoms were measured using standard questionnaires such as the 17-item Hamilton Depression Rating Scale (HAMD-17), the Beck Depression Inventory-21 (BDI), and the 14-item Hamilton Anxiety Rating Scale (HAMA) prior to the 4 week trial and afterwards. When comparing the depression and anxiety score between week zero (baseline) and week 4 (study endpoint), results showed a significant reduction in reported symptoms on all three measures. The findings suggest that transcranial bright light therapy might be an alternative to the traditional light therapy and should be explored in more depth.

12. Encephalopsin (OPN3) protein abundance in the adult mouse brain.

Authors: Nissilä J, Mänttäri S, Särkioja T, Tuominen H, Takala T, Timonen M, Saarela S.

Journal: J Comp Physiol A Neuroethol Sens Neural Behav Physiol. 2012 Nov;198(11):833-9

Summary: The presence of light-sensitive opsins in the retina has been shown successfully in various studies. The present study investigates the expression encephalopsin (OPN3) proteins in brain and peripheral tissue of mice. Tissue samples of 10 mice were analysed using Western blotting and immunohistochemistry. Results showed the OPN3 protein expression could be shown in almost all brain areas as well as in the peripheral tissue analyzed. This suggests that OPN3 might be involved in the mechanism of transcranial bright light.

13. Group-ICA model order highlights patterns of functional brain connectivity.

Authors: Abou-Elseoud A, Littow H, Remes J, Starck T, Nikkinen J, Nissilä J, Timonen M, Tervonen O, Kiviniemi V.

Journal: Front Syst Neurosci 2011;5(37):1-17

Summary: 90 subjects (45 SAD patients; 45 healthy controls) underwent a fMRI to determine functional connectivity of brain areas. Results from the fMRI scans were analyzed with different mathematical models. In addition to increased neuronal connectivity within the visual and senso-motoric cortex of the SAD patients, results showed that depending on the model order and analysis, the sensitivity towards disease detection can be significantly improved and resting state brain activity might prove to be a very useful tool to detect the underlying neurobiological substrates of diseases.

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