Summary of published, peer-reviewed findings
Valkee Oy (November 2014)

Research efforts at Valkee follow a two-fold focus: Showing clinical effectiveness of the treatment while at the same time investigating the underlying mechanism of action of transcranial bright light.

The following results have been published in international, peer-reviewed journals:

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

Autoren: Jurvelin H, Takala T, Nissilä J, Timonen M, Rüger M, Jokelainen J, Räsänen P
Journal: BMC Psychiatry
Pub Med link: http://www.ncbi.nlm.nih.gov/pubmed/25330838

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 in the ear 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

2. 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 Aug;31(7):855-60. doi: 10.3109/07420528.2014.916297. Epub 2014 May 14.
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/24828616

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).

3. 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 May 12;5:184. doi: 10.3389/fphys.2014.00184. eCollection 2014.
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/24860513

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.

4. 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.
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/22296809

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.

5. 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.
Journal link:
http://www.scirp.org/journal/paperinformation.aspx?paperid=19417#.UtwENhA1iM8

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), summarized below.

6. 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, Tervonen O, Timonen M, Kiviniemi V.

Journal: Hum Brain Mapp. 2014 Jan;35(1):161-72.
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/22987670

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 in the previous study.

7. 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.
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/21687724

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.

8. 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
PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/22991144

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.

Summary of published studies
2013

1. 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, 78:511-515.

Summary
Explorative pilot study about the effects of transcranial Light for treating symptoms of winter depression (SAD). 13 patients with SAD - Seasonal Affective Disorder (DSM-IV-TR criteria used) participated in the study which lasted four weeks. During the study they received an 8-12 minutes dose of transcranial bright light therapy in the morning five days a week . The symptoms of the patients were recorded by standardized tests (Hamilton Depression Rating Scale (HAMD-17), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAMA)). At the end of the study 76% of the patients showed a complete remission of their symptoms and 92% of patients showed a 50% improvement of their symptoms.

This information was presented as a poster at the following conference:
Poster presentation at International Forum on Mood and Anxiety Disorders (IFMAD) 9.-11.2011, Budapest, Hungary
Timonen M, Nissilä J, Liettu A, Jokelainen J, Jurvelin H, Aunio A, Räsänen P, Takala T.
Transcranial Brain Targeted Light Treatment via Ear Canals in Seasonal Affective Disorder (SAD) – a Pilot Study.

2. 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, Jokelainen J, Räsänen P.
Journal: submitted at Behavioral and Brain Functions – Journal

Summary

A randomized four-week study focused on comparing the clinical effectiveness of three kinds of transcranial bright light doses (1, 4, 9 lumen) on 89 patients with severe seasonal affective disorder. The subjects received one of the three transcranial bright light doses in the morning. The symptoms of depression have been checked at the beginning, during the study and at the end of the study; the cognitive performance has been checked at the beginning and at the end of the study by using Trail Making Tests (TMT). The remission rate for all three groups was 74-79% for symptoms of seasonal affective disorder and 47-62% for symptoms of anxiety (in each case at least 50% reduction of the BDI-21 and HAMA result in the fourth week). The cognitive performance also significantly improved in all three groups at the end of the study compared to the beginning of the study.

This information was presented as a poster at the following conference:
Poster presentation at International Forum on Mood and Anxiety Disorders (IFMAD) 9.-11.2011, Budapest, Hungary. Jurvelin H, Takala T, Nissilä J, Timonen M, Jokelainen J, Räsänen P. *Transcranial bright light treatment via ear canals in seasonal affective disorder: a randomized controlled double-blind dose-response study*

3. 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 divided randomly into two groups (N=24 experimental condition; N=26 controlled condition) and received either 12 min transcranial bright light therapy or sham therapy, i.e. no light. At the same time they underwent a functional magnetic resonance tomography. The results of the fMRT showed a clear activation of the visual cortex and sensorimotor brain areas during transcranial light exposure in contrast to the sham group. This is a sign of general light sensitivity of the brain.

This information was presented as a poster at the following conference:
Poster presentation in ISMSM 7-13 May 2011 Montreal, Canada.
Starck T, Nissilä J, Aunio A, Abou-Elseoud A, Remes J, Nikkinen J, Timonen M, Takala T, Tervonen O, Kiviniemi V. *Stimulating brain tissue with bright light -resting state fMRI analysis.*

4. 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 patients with seasonal affective disorder and 45 healthy control subjects) underwent an fMRI to determine the functional connections of brain areas. At the end of the study the functional connections in their brains have been analyzed by using different

mathematical models. The results showed that the sensitivity to detect diseases can be increased depending on the model order and the analysis.

5. The function of brain neural networks in patients suffering from SAD and effect of transcranial light exposure on brain neural networks.

Authors: Abou Elseoud A, Starck T, Nissila J, Liettu A, Jokelainen J, Takala T, Aunio A, Nikkinen J, Remes J, Koponen H, Tervonen O, Timonen M, Kiviniemi V.
Journal: Manuscript not yet finished, summary relates on the congress abstract.

Summary
90 subjects (45 patients with seasonal affective disorder and 45 healthy control subjects) were scanned and their functional connections in the brain areas determined by using fMRI. In addition, 50 further subjects were scanned, which have been randomly divided into two groups (N = 24 experimental group, N = 26 control group). They received either transcranial light or a placebo. The results showed that the increased functional connection in the visual and sensorimotor brain area, which was found within the group of seasonal affective disorder patients also showed up in the experimental group, but not in the placebo group.

This information was presented as a lecture at the following conference:
Society Scandinavian Physiological Society (SPS) congress 24.-26.8.2012 in Helsinki, Finland. Elseoud A, Starck T, Nissila J, Liettu A, Jokelainen J, Takala T, Aunio A, Nikkinen J, Remes J, Koponen H, Tervonen O, Timonen M, Kiviniemi V.
Functional connectivity alterations in seasonal affective disorder overlap with extravisual light therapy effects. Acta Physiol 2012, 206(S691)

6. 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
Several studies now confirmed the appearance of light-sensitive opsins in the retina. The present study investigates the appearance and amount of encephalopsin and melanopsinprotein in the brain and the periphery. For this purpose, samples of brain tissue were taken of ten mice to determine the appearance of encephalopsin and melanopsin protein by using the Western Blotting technique; the samples originated of different regions of the brain and the periphery. It turned out, that encephalopsin as well as melanopsin proteins were found in almost all regions of the brain and in the periphery. This is a sign for the general light sensitivity of the brain and would explain the efficacy of transcranial bright light therapy.

This information was presented as a poster at the following conferences:
Poster presentation in the 20th European Congress of Psychiatry (EPA), Prague, Czech Republic, 3-6 March, 2012: Nissila J, Mänttäri S, Tuominen H, Särkioja T, Takala T, Timonen M, Saarela S.
The abundance and distribution of melanopsin (OPN4) protein in the human brain.

Poster presentation in Society Scandinavian Physiological Society (SPS) 24.-26.8.2012 in Helsinki, Finland: Nissila J, Mänttäri S, Tuominen H, Särkioja T, Takala T, Timonen M,

Saarela S. *The abundance and distribution of encephalopsin (OPN3) protein in the human brain.* Acta Physiol 2012,206(S691)

7. Effects of bright light treatment on psychomotor speed in top level athletes: Randomized, Double-blind, placebo-controlled study

Author: Tullpo, M
Journal: Manuscript submitted

Summary:
22 pro-hockey players from Finland (Team Oulu Kärpät; 11 = control group; 11 = experimental group) received during the most intensive phase of the Hockey League (in October) for 24 days in the morning either 12 minutes of transcranial light or a placebo. Before the beginning of the study and after, the reaction time of the athletes was determined by using a reaction time test. The test distinguished between moving reaction time, i.e. the period of action potential for finger lifting, and overall response time. It turned out that the movement reaction time to the alarm signal was significantly improved in the light group compared to the placebo group, whereas as far as the overall response time is concerned, there could not be determined any difference between the groups.

This information was presented as lectures at the following conferences:
Oral presentation in Society Scandinavian Physiological Society (SPS) 24.-26.8.2012 in Helsinki.
Tulppo M.
Effects of bright light treatment on psychomotor speed in top level athletes: Randomized, Double-blind, placebo-controlled study. Acta Physiol 2012, 206(S691). Manuscript submitted.

Oral presentation in Society for Light Treatment and Biological Rhythm (SLTBR), 24.-27.6.2012 Geneva, Switzerland: Tulppo M. Effects of bright light treatment on psychomotor speed in top level athletes: Randomized, Double-blind, placebo-controlled study.

8. Does light have psychophysiological non-image forming effects outside of retinohypothalamic tract?

Authors: Jurvelin H, Nissilä J, Kallio L, Saarela S, Vakkuri O, Leppäluoto J, Tulppo M, Starck T, Kiviniemi V, Takala T
Journal: Manuscript not yet submitted

Summary:
Bright light studies show that light has antidepressant effects, independent of the suppression of melatonin. The following study investigates whether the effect of transcranial light is mediated by melatonin. 8 healthy subjects received in a placebo-controlled, cross-over protocol during the night (at one o'clock) both 24 min transcranial light and 24 min placebo. The melatonin concentration in the saliva was determined before, during, and after the light or

placebo exposure. The results showed no difference in the melatonin concentration between the experimental and the placebo group, which indicates that the mood-enhancing effects of transcranial light are not mediated by the suppression of melatonin.

This information was presented as a poster at the following conference:
Poster presentation in the 12th International Forum on Mood and Anxiety Disorders (IFMAD), Barcelona, Spain, November 7-9th 2012: Jurvelin H, Nissilä J, Kallio L, Saarela S, Vakkuri O, Leppäluoto J, Tulppo M, Starck T, Kiviniemi V, Takala T. Does light have psychophysiological non-image forming effects outside of retinohypothalamic tract?

9. The Effect of bright light treatment via ear canals on attention as measure of neurophysiology – a Randomized Controlled Study

Authors: Jurvelin H, Nissilä J, Havo M, Timonen M, Jokelainen J, Kiviniemi V, Tulppo MP, Roivainen E, Takala T.
Journal: Manuscript not yet finished. Summary relates on the abstract

Summary:
Transcranial bright light has antidepressant effects and modulates the neural networks of the human brain. 41 students were randomly divided into two groups and received for three weeks either 12 min transcranial bright light or placebo in the morning. At the beginning and the end of the study cognition (recognition test; Cognitspeed, Finland) and the depressive symptoms (BDI) of the subjects were determined. The third week showed a significant improvement of the cognitive performance and the depressive symptoms in the experimental group compared to the beginning (week 1). Within the control group there were no changes in cognition and depressive symptoms between the first and the third week.

This information was presented as a poster at the following conference:
Poster presentation in Society Scandinavian Physiological Society (SPS) 24.-26.8.2012 in Helsinki. Jurvelin H, Nissilä J, Havo M, Timonen M, Jokelainen J, Kiviniemi V, Tulppo MP, Roivainen E, Takala T. *The Effect of bright light treatment via ear canals on attention as measure of neurophysiology – a Randomized Controlled Study*. Acta Physiol 2012,206(S691)

10. Effects of transcranial bright light treatment on cardiovascular autonomic regulation.

Authors: Tulppo MP, Kiviniemi AM, Hautala AJ, Karjalainen J, Jaakkola JJ, Ikaheimo TM, Nissila J, Jurvelin H, Takala T, Huikuri HV.
Journal: Manuscript not yet finished; summary relates on the abstract

Summary:
19 drug-free men with mild hypertension received during a placebo-controlled, cross-over study in the morning 12-min transcranial bright light as well as 12 min placebo. Before, during, and after the bright light and placebo exposure the blood pressure and ECG were measured and the standard parameters of the heart rate variability were determined. It was found that transcranial bright light has increased the heart rate variability, which indicates a greater adaptability of the autonomic system during stress, a phenomenon which is generally reduced in hypertensive patients.

This information was presented as a poster at the following conference:
-Poster presentation in The European Association for Cardiovascular Prevention And Rehabilitation (EARCP) annual meeting Rome Italy 18-20 April 2013. Tulppo MP, Kiviniemi AM, Hautala AJ, Karjalainen J, Jaakkola JJ, Ikaheimo TM, Nissila J, Jurvelin H, Takala T, Huikuri HV. *Effects of transcranial bright light treatment on cardiovascular autonomic regulation.*

11. Transcranial light exposure acutely alleviate anxiety symptoms in mildly depressed partcipants- A randomized, sham- controlled, double-blind trial

Authors: Heidi Jurvelin, Markku Timonen, Johanna Lammi, Jari Jokelainen, Melanie Rueger, Timo Takala

Summary:
Traditional bright light therapy has been successfully proven for treating anxiety symptoms in SAD patients as well as in healthy people who complain of increased anxiety symptoms. The following study investigated whether transcranial bright light acts acutely anxiolytic (anxiety reducing) in subjects with a higher level of anxiety symptoms.
28 subjects (F=19, M=9, average age ± SD: 44 ± 14 years) took part in the study and were divided randomly into to two groups. One group received 12 min transcranial bright light via the ear (experimental group), whereas the other group received no light (sham group). All tests took place in the morning between 9 and 12 o'clock. The anxiety symptoms were determined 5 minutes before and 10 minutes after the bright light treatment by using a standardized questionnaire (STAI; Spielberger State-Trait Anxiety Inventory, form Y1). In the experimental group there was a significant reduction of anxiety symptoms by 12.1 ± 7.3 % from 43.7 ± 2.0 points before the bright light treatment to 38.1 ± 1.4 points after the bright light treatment, whereas there was no change in the sham group (before bright light treatment: 45.6 ± 2.2, after the bright light treatment: 43.4 ± 1.7).

This information was presented as a poster at the following conference:
Poster presentation in the 13th International Forum on Mood and Anxiety Disorders (IFMAD), Monaco, November 20-22th 2013