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Light therapy and serotonin transporter binding in the anterior cingulate and prefrontal cortex

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Abstract

Objective—To investigate the effects of light therapy on serotonin transporter binding (5-HTT BP_{ND}), an index of 5-HTT levels, in the anterior cingulate and prefrontal cortices (ACC and PFC) of healthy individuals during the fall and winter. Twenty-five per cent of healthy individuals experience seasonal mood changes that affect functioning. 5-HTT BP_{ND} has been found to be higher across multiple brain regions in the fall and winter relative to spring and summer, and elevated 5-HTT BP_{ND} may lead to extracellular serotonin loss and low mood. We hypothesized that, during the fall and winter, light therapy would reduce 5-HTT BP_{ND} in the ACC and PFC, which sample brain regions involved in mood regulation.

Method—In a single-blind, placebo-controlled, counterbalanced, crossover design, [^{11}C]DASB positron emission tomography was used measure 5-HTT BP_{ND} following light therapy and placebo conditions during fall and winter.

Results—In winter, light therapy significantly decreased 5-HTT BP_{ND} by 12% in the ACC relative to placebo ($F_{1,9}$ = 18.04, P = 0.002). In the fall, no significant change in 5-HTT BP_{ND} was found in any region across conditions.

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Declaration of interest

Drs. Meyer, Wilson, and Houle have received operating grant funding for other studies from Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Lundbeck, SK Life Science, and Johnson and Johnson in the past 5 years. With the exception of Johnson and Johnson, Dr. Meyer has consulted to these companies, as well as Sepracor, Trius Therapeutics, Teva and Mylan Inc. None of these companies participated in the funding, design, or execution of this study or writing the manuscript. Dr. Meyer is developing natural health products to treat high-risk states for MDE. Dr. Meyer is applying for patents to implement measures utilizing MAO to diagnose or treat mood disorders and to use peripheral measures as surrogate measures for brain inflammation. Dr. Sarah Harrison was employed by INC research, Forest Laboratories and Janssen, Pharmaceutical Inc., during the past 2 years. All other authors have no declaration of interest.

Conclusion—These results identify, for the first time, a central biomarker associated with the intervention of light therapy in humans which may be applied to further develop this treatment for prevention of seasonal depression.

Keywords

light therapy; serotonin transporter; serotonin; anterior cingulate cortex; seasonal affective disorder

Introduction

In 2008, the World Health Organization (WHO) identified major depressive disorder (MDD) as the leading cause of death and disability in moderate to high income nations (1) indicating that new prevention methods are needed. One subtype of MDD, seasonal affective disorder (SAD), has a 1–6% prevalence rate, depending on latitude and ethnicity (2), and 40% of people who experience SAD eventually develop MDD, thereby further contributing to the burden of MDD (3–5). There is additional reason to study the seasonal impact upon mood as 25% of healthy individuals experience seasonally related changes in mood, energy, appetite, and sleep that affect daily function (6–10). Given the high prevalence of SAD, its role in predisposing to MDD, and the common problem of impaired function from seasonal variation in mood, it is important that better prevention and treatment strategies be developed.

Direct investigation of prevention strategies through clinical trials is labor intensive as only a subset of individuals develops SAD. Similarly, direct investigation of treatment strategies with large-scale clinical trials is also difficult as these trials must be oriented to the winter months. Hence, a valuable intermediate approach is to develop biomarkers to assess the effect of intervention strategies. The magnitude of effect of the intervention strategy on the biomarker may be applied to identify therapeutics that should be carried forward in development. One candidate biomarker for this approach is the serotonin transporter binding potential (5-HTT BP_{ND}), as measured with carbon 11–labeled 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]DASB) positron emission tomography (PET). 5-HTT BP_{ND} equals the ratio of specifically bound to free and non-specifically bound [^{11}C]DASB in tissue at equilibrium and is an index of serotonin transporter protein (5-HTT) levels (11–13). In addition, 5-HTT BP_{ND} fluctuates with season at latitudes where SAD is substantially prevalent. For example, in a study of 5-HTT BP_{ND} with [^{11}C]DASB PET in 88 healthy volunteers in Toronto, Canada, markedly elevated 5-HTT BP_{ND} occurred in fall/winter as compared to spring/summer in a number of affect-modulating brain regions including the anterior cingulate and prefrontal cortices (ACC and PFC, respectively), as well as the thalamus and midbrain (11). In a subsequent study in Copenhagen, Denmark, Kalbitzer et al., applied [^{11}C]DASB PET and replicated the seasonal variation in 5-HTT BP_{ND} in 54 subjects (13). [^{11}C]DASB PET has major advantages over previous PET radiotracers used to measure 5-HTT BP_{ND}, including excellent selectivity, good reversibility and a better specific to free and non-specific binding ratio. Nevertheless, similar results were also found in applications with other imaging techniques: in Amsterdam, Ruhe et al., applied [^{123}I]β-CIT single-photon emission tomography and noted the same relationship between midbrain 5-HTT BP_{ND} and season in a sample of 49 healthy

and 49 depressed subjects (14) while Buchert et al., in Hamburg, Germany, used [^{11}C]McN5652 PET in 39 subjects and reported the season-related finding in the midbrain, but not in the thalamus (15). Collectively, these findings indicate that 5-HTT BP_{ND} is higher across multiple brain regions in fall/winter months compared with spring/summer.

Most 5-HTT is located at outer cell membranes, mainly perisynaptically, but also along axons and intracellularly (16). DASB has been observed to have a strong preferential binding to 5-HTT on outer cell membranes (12). As such, it is likely that changes in 5-HTT binding (5-HTT BP_{ND}) observed *in vivo* using [^{11}C]DASB PET substantively reflect 5-HTT protein levels at the cell surface where 5-HT reuptake occurs (12). The important physiological role of 5-HTT on mood regulation is attributable to its influence on extracellular 5-HT levels (12, 17–24): there is an inverse relationship between available 5-HTT and clearance of extracellular 5-HT as 5-HT reuptake inhibitor antidepressants raise extracellular 5-HT (18, 19), 5-HTT knockout mice have greater extracellular 5-HT (22, 23), and mice with overexpression of 5-HTT have low extracellular 5-HT (24). In addition, in humans, lowering 5-HT via acute tryptophan depletion (25) is associated with low mood, particularly in those vulnerable to developing major depressive episodes (MDE) such as those with family histories of MDE, or past histories of MDE (26–28). Furthermore, 5-HT levels and/or their neuromodulatory role are strongly implicated in mood disorders, given the many selective serotonin reuptake inhibitors (SSRIs) that raise extracellular serotonin are associated with amelioration of depressive symptoms in individuals suffering from MDD (29, 30). Modulators of extracellular 5-HT are important because it is well established that 5-HT plays a role in physiology and behaviours reported to change with season including mood, sleep, appetite, and energy (31). Taken together, these findings emphasize that the importance of the 5-HTT, in regards to affect-regulation, is its influence on extracellular serotonin levels.

The purpose of this study was to investigate the effect of a standard intervention for SAD treatment, light therapy (32) on a potential therapeutic biomarker, 5-HTT BP_{ND}. In both studies of seasonal variation in 5-HTT BP_{ND} using [^{11}C]DASB PET, an inverse correlation between duration of daily sunlight and 5-HTT BP_{ND} was found, suggesting that this might be a promising biomarker for light therapy (11, 13). Our hypothesis was that the administration of light therapy during the fall and winter months would reduce 5-HTT BP_{ND} in the anterior cingulate and prefrontal cortices (ACC and PFC). The ACC and PFC (and/or subregions of these structures) are often activated in mood induction studies (reflecting processes that generate sad mood) (33–35), and they also participate in cognitive functions such as those leading to pessimism that create a sad mood (36, 37). Other regions including the thalamus, basal ganglia, hippocampus, and midbrain were also examined because 5-HTT density is high in these regions (38–40).

Aims of the study

Our primary aim was to investigate the effect of light therapy on serotonin transporter binding in the anterior cingulate and prefrontal cortices of healthy individuals during the fall and winter using a single-blind, placebo-controlled, counterbalanced, crossover design. We used PET with the radioligand [^{11}C]DASB to measure serotonin transporter binding, an

index of serotonin transporter levels, in these brain regions following light therapy and placebo conditions. We hypothesized that serotonin transporter binding would be reduced after light therapy as compared to placebo treatment in these brain regions.

Material and methods

Participants

Twenty-one healthy volunteers [11 women and 10 men; mean (SD) age 25.8 (5.8) years; age range 19–39] were recruited through fliers posted in community locations within the Toronto area. We elected to study healthy volunteers, rather than SAD patients because we were interested in investigating the potential of 5-HTT BP_{ND} as a biomarker for light exposure, so as to develop prevention strategies for those who had not yet developed SAD. This was plausible because previous observations of correlations between 5-HTT BP_{ND} and season were in healthy samples (11, 13). For each participant, written informed consent was obtained after the procedures were fully explained. The study and recruitment procedures were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, University of Toronto. Participants were recruited as non-smoking healthy volunteers, with no history of major medical or psychiatric illness, no history of alcohol or substance abuse and no recent use of prescription or over the counter medications, including herbal supplements. Female subjects were free from oral contraceptives. Subjects were screened using the structured clinical interview for DSM-IV–non-patient edition to rule out psychiatric disorders (current or in remission), current suicidal ideation, history of self-harm, anger dyscontrol or impulsive behaviour. Urinalysis and urine drug screening were also performed to rule out recent herbal, drug, or medication use (i.e., within five half-lives).

Two subjects did not complete the study. One subject withdrew due to discomfort in the scanner. A second subject had a positive urine drug screen for a recreational drug and was subsequently withdrawn. Thus, between October 2009 and March 2010, 19 participants (10 women and nine men) completed the study.

Study design

Volunteers participated in a single-blind, placebo-controlled, within-subject, counterbalanced, crossover design. All subjects completed two experimental conditions separated by a 4-week washout period. In Condition 1, participants received five sessions of daily light therapy, and in Condition 2, participants received five sessions of placebo treatment. In each treatment condition, sessions were 30 min in length and took place between 7:00 am and 7:30 am for five consecutive mornings. Subjects were randomly assigned to the order in which they received each condition.

Condition 1 (light therapy)—Subjects were seated approximately 30 cm in front of a Day-Light Classic light box (Uplift Technologies Inc., Dartmouth, NS, Canada), which emitted broad-spectrum fluorescent white light at 10 000 lux for 30 min; the standard treatment dose for SAD (41, 42). The height of the box was adjusted so that the subject's eyes were level with the center of the screen, and the box was tilted at an angle of

approximately 15° downward. During the sessions, subjects were asked to read so that gaze was cast downward and head position and posture were monitored by study investigator SJH.

Condition 2 (placebo)—In a room separate from that in which subjects had undergone the light therapy condition, subjects were tethered to an inactive negative ionization system (Sphere One Inc., Chattanooga, TN, USA) with a Velcro wrist strap and seated approximately 30 cm in front of the ionizer. Posture and position were monitored by study investigator SJH. To control for expectancy bias, this intervention was described as another active condition. Subjects were instructed to read for the duration of the 30-min session.

Mood-related symptoms were assessed at screening and on day 5 of each condition using the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS), Beck Depression Inventory (BDI), and the 10-cm Visual Analogue Scale (VAS) for mood (i.e., happy–depressed), energy (i.e., most–least), and anxiety (i.e., relaxed–tense). At the end of each condition, subjects also underwent a [^{11}C] DASB PET scan to measure 5-HTT BP_{ND}.

Image acquisition and analysis

Participants underwent a [^{11}C]DASB PET scan at the end of each treatment condition, spaced a minimum of 4 weeks apart. All scans were scheduled for the morning and took place at either 9:30 am or 11:30 am. Lighting conditions in the scan room were kept constant during scanning and participants were instructed to keep their eyes closed for the scan duration. Participants were required not to consume any caffeine or alcohol 48 h prior to scanning. On the day of scanning, subjects also underwent laboratory tests (complete blood cell count, plasma sampling for calcium, cotinine, and thyroid hormones) to ensure physical health and non-smoking status and a urine drug screen to rule out recent herbal, drug, or medication use (within five half-lives). All subjects were medication free prior to scanning, save for three participants who tested positive for over the counter medications, none of which seemed likely to influence the serotonin transporter (ibuprofen, aspirin, and pseudoephedrine). In addition, removal of these subjects from analysis did not affect the significance of the results and therefore, these data were included in the final analyses.

Synthesis and measurement of 5-HTT BP_{ND} with [^{11}C]DASB reported in this study are the same as those used in previous studies (11, 43–50). Briefly, PET images were acquired using a high-resolution research tomograph (HRRT) PET camera (in-plane resolution; full width at half maximum, 3.1 mm; 207 axial sections of 1.2 mm; Siemens Molecular Imaging, Knoxville, TN, USA). Prior to each scan, an intravenous bolus of 10 mCi (370 MBq) of [^{11}C]DASB was injected. The [^{11}C]DASB was of high radiochemical purity (99.35 ± 0.57%) and high specific activity (84.78 ± 31.14 GBq/μmol) at the time of injection. The emission scan was reconstructed in 15 frames of 1 min, followed by 15 frames of 5 min, totaling to a scan duration of 90 min in length (43, 51). The images were corrected for attenuation using a cesium 137–labeled transmission scan and reconstructed by filtered back projection (Hann filter), and additional details regarding the scanning acquisition have been previously published (50). Each participant also underwent magnetic resonance imaging

(GE Signa 1.5-T scanner, spin-echo sequence proton-density-weighted image, *x, y, z* voxel dimensions; 0.78, 0.78, and 3 mm, respectively; GE Medical Systems, Milwaukee, WI, USA) for the region of interest (ROI) delineation. ROIs were delineated on these magnetic resonance images using a semi-automated method based on linear and nonlinear transformations of an ROI template in standard space to each individual magnetic resonance image (MRI), followed by a refinement process based upon the gray matter probability (52). The MRI was coregistered to the summated [^{11}C]DASB PET image using a mutual information algorithm (53), and the resulting transformation was applied to sample the ROIs from the PET image. The location of the ROI was verified by visual assessment on the summated [^{11}C]DASB PET image. The posterior half of the cerebellar cortex under exclusion of vermis and cerebellar white matter served as the reference region. The borders of the reference tissue were at least one full width at half maximum (5.5 mm) from the venous sinuses and occipital cortex. At a distance of one full width at half maximum, spillover from the occipital cortex (which has specific binding) or the venous sinuses is negligible.

5-HTT BP_{ND} values were determined using the non-invasive Logan method (PMOD Technologies Ltd., Zurich, Switzerland) (54). This method provides valid and reproducible [^{11}C]DASB PET measurements of 5-HTT BP_{ND} values with low between-subject variance in 5-HTT BP_{ND} for most brain regions (45, 47–49). A secondary analysis was conducted using the simplified reference tissue method 2 (SRTM2) (51, 55).

Statistical analysis

Participants were divided into fall (September 22 to December 20) and winter (December 21 to March 19) groups corresponding to the season in which they were scanned. The mean scan date (SD) of the fall group was November 17, 2009 (18.6 days), and the mean scan date of the winter group was February 13, 2010 (16.1 days).

For each region, within each group, the Shapiro–Wilk test was applied to assess the normality of the distribution of the difference in 5-HTT BP_{ND} between light and placebo conditions. PET data were also plotted as a histogram for each group and visually inspected to ensure normality and concordance with the Shapiro–Wilk test. In the fall group, the difference in 5-HTT BP_{ND} between light and placebo was normally distributed across all brain regions assayed. In the winter group, PET data were normally distributed across all brain regions with the exception of the thalamus (Shapiro–Wilk test, $W = 0.82$, $P = 0.03$).

The primary analyses were repeated-measures multivariate analyses of variance (MANOVA) applied to each group to assess the effect of treatment (light therapy vs. placebo) on 5-HTT BP_{ND} (the repeated dependent variable) in the ACC and PFC within each season. Regional univariate repeated-measures ANOVAs were applied only if there was a significant omnibus effect in the repeated-measures MANOVA. To correct for four multiple comparisons (two seasons, fall and winter; two *a priori* brain regions, ACC and PFC), significance for each ANOVA was set at a *P*-value of 0.0125. As a secondary analysis, for each group, a repeated-measures MANOVA was applied to assess for a global effect of treatment (light therapy vs. placebo) on 5-HTT BP_{ND} in all brain regions assayed, with the exclusion of data from the thalamus pertaining to the winter group, which was not normally distributed.

In addition, for each group, exploratory two-tailed paired *t*-tests were also performed to examine the effects of treatment in all brain regions, with the exception of winter data from the thalamus, for which the nonparametric Wilcoxon signed-ranks test was applied. For these exploratory analyses, to correct for 14 multiple comparisons (two seasons, fall and winter; seven brain regions), significance was set at a *P*-value of 0.0036. For each group (with the exclusion of winter data from the thalamus), effect size (Cohen's *d*) was calculated for all regions, defined as mean difference across conditions (light vs. placebo) divided by the standard deviation of the difference across conditions. For winter data from the thalamus, effect size was calculated by dividing the test statistic from the nonparametric Wilcoxon signed-ranks test by the square root of the number of observations.

As an additional exploratory measure, Pearson's correlation coefficients were also applied to determine whether there was a relationship between reduction in 5-HTT BP_{ND} in the ACC, a region heavily involved in mood regulation (56), following light therapy relative to placebo, and improvement on scales of mood-related symptoms (BDI, VAS mood, anxiety, energy, and SIGH-ADS). All analyses were performed using the Statistical Package for Social Sciences version 20 (IBM SPSS Statistics, Chicago, IL, USA).

Results

In the winter group, there was a main effect of treatment on 5-HTT BP_{ND} in the ACC and PFC (repeated-measures MANOVA, $F_{2,8} = 19.54$, $P = 0.001$). Subsequent univariate pairwise ANOVAs showed this treatment effect to be significant only in the ACC ($F_{1,9} = 18.04$, $P = 0.002$) after correction for multiple comparisons where a decrease in 5-HTT BP_{ND} of 12% was observed following light therapy relative to placebo, but not in the PFC (magnitude −1.1%, $F_{1,9} = 0.23$, $P = 0.64$). As a secondary analysis, the repeated-measures MANOVA was rerun with all ROIs, excluding the thalamus, and an effect of treatment was observed ($F_{4,6} = 14.53$, $P = 0.01$); however, as this was an exploratory analysis among a number of such analyses, greater than 5, this was viewed as a non-significant finding. Subsequent exploratory *t*-tests revealed some level of reduction in 5-HTT BP_{ND} in the ventral striatum after light therapy compared with placebo (magnitude −9.9%, paired *t*-test, $t_9 = 2.85$, $P = 0.02$) and hippocampus (magnitude −10%, paired *t*-test, $t_9 = 1.73$, $P = 0.12$), but the effect in the ventral striatum did not remain significant after correction for multiple comparisons (Fig. 1 and Table 1). In addition, in the winter group, upon application of the two-tailed nonparametric Wilcoxon signed-ranks test, we did not observed a significant effect of treatment (light therapy vs. placebo) on 5-HTT BP_{ND} in the thalamus ($Z = -1.79$, $P = 0.08$). In the fall group, there was no significant effect of treatment on 5-HTT BP_{ND} observed in the ACC and PFC (repeated-measures MANOVA, $F_{2,7} = 0.93$, $P = 0.44$) or, upon additional comparison, in any other examined region (Table 1). Similar results were obtained when analyzing 5-HTT BP_{ND} values obtained from applying SRTM2. 5-HTT BP_{ND} values were highly correlated across the two methods in each region, within both light therapy and placebo conditions (Pearson's correlation coefficient, $r = 0.90–0.99$, $P \leq 0.001$ and $r = 0.92–0.99$, $P \leq 0.001$ respectively).

An exploratory analysis was also conducted to determine whether there was a relationship between reduction in 5-HTT BP_{ND} in the ACC following light therapy relative to placebo

and improvement of mood-related symptoms. As small changes in mood-related symptoms would be expected of healthy subjects prior to and after light therapy, behavioural data were pooled across fall and winter groups ($n = 19$) to increase statistical power. Accordingly, a modest positive, trend-level correlation was observed between reduction in 5-HTT BP_{ND} in the ACC following light therapy relative to placebo and improvement of scores on the BDI (Pearson's correlation coefficient, $r = 0.45$, $P = 0.06$) and VAS mood (Pearson's correlation coefficient, $r = 0.34$, $P = 0.16$). However, no significant or trend-level correlations were observed between the other scales of mood symptoms (VAS anxiety, energy, or SIGH-ADS) and change in 5-HTT BP_{ND} in the ACC or PFC.

We also collected sleep data via actigraphy (Actiwatch Spectrum, Philips Respironics, Pennsylvania, USA) because we were interested in investigating the relationship between changes in sleep measures and in 5-HTT BP_{ND} following light therapy. However, we did not observe a significant correlation between change in ACC 5-HTT BP_{ND} and any sleep measure (time of awakening, bed-time, number of awakenings, sleep duration, sleep efficacy, and sleep latency, $r = 0.20–0.04$, $P = 0.40–0.87$) across conditions and upon further analysis and did not find group differences in changes in these parameters (Table 2). Most likely, the reason for this was that the sample had fairly normative levels of these measures.

Discussion

This is the first investigation to compare the effect of light therapy to placebo upon 5-HTT BP_{ND} in the human brain. The primary finding is that, during the winter, administration of light therapy significantly decreased 5-HTT BP_{ND} in the ACC of healthy humans, and this reduction remained significant after correction for multiple comparisons. In the fall group, no significant change was observed in any examined brain region. These results have important implications as they suggest a novel mechanism by which light exposure may exert an antidepressant effect and also provide a basis upon which to better develop light therapy for prevention of SAD.

At present, there is no consensus by which light therapy facilitates amelioration of depressive symptoms such as low mood. However, the finding that light therapy, a first-line treatment for SAD, affects 5-HTT BP_{ND} in the ACC is in accordance with literature supporting the role of this brain region in regulation of mood and antidepressant response. The ACC participates in production of sad emotions, where regional activations occur during transient sadness and a reduction in activity follows recovery from depression (35). In addition, activity in the ACC has been observed to decrease in response to antidepressant drug treatment, cognitive behavioural therapy, transcranial magnetic stimulation, and deep brain stimulation (DBS) (56). Interestingly, 5-HT function in the ACC may be important for treatment response as, in rodent models of depressive behaviour, 5-HT depletion abolishes the antidepressant effects of DBS in the ACC (57, 58).

One explanation for reduced 5-HTT BP_{ND} in the ACC following light therapy is that, during the winter, light exposure may increase signaling between the retina, dorsal raphe nucleus (DRN) of the midbrain and ACC to influence 5-HTT BP_{ND} in the ACC. To elaborate upon this putative mechanism, it has been reported that retinal sensitivity, as measured by

electroretinography, changes after light therapy in individuals with SAD (59) and also varies seasonally in both subsyndromal and full-syndrome SAD (59, 60). In addition, in a recent preclinical study, it was shown that, following light exposure, a distinct population of non-visual DRN-projecting retinal ganglion cells (RGCs) was able to modulate affective behaviour via increased input to 5-HT neurons in the DRN (61). Furthermore, in rodents, sleep deprivation, an antidepressant treatment that increases neuronal firing in the DRN (62), has been found to downregulate levels of monoamine transporters such as the 5-HTT and norepinephrine transporter (NET) in efferent limbic structures (63, 64). The DRN has projections to the ACC (65) and 5-HTT BP_{ND} in the ACC varies inversely with duration of daily sunshine (11). In future study, preclinical investigation would be helpful in regards to identifying specific cellular mechanisms underlying this light-induced change in 5-HTT BP_{ND}.

As approximately 25% of healthy individuals experience seasonal changes in mood and energy that impair functioning (6–10) and only 55% of individual suffering from seasonal depressive symptoms fully remit after light therapy (66), there is an urgent need for research to optimize this treatment for prevention of SAD. [^{11}C]DASB PET is currently applied to guide new antidepressant drug development for medications that bind to the 5-HTT (45–47, 67, 68). Our finding of a decrease in 5-HTT BP_{ND} in the ACC of healthy individuals and an associated increase in mood after light therapy represents the first central biomarker associated with therapeutic response to light exposure. This reduction in 5-HTT BP_{ND} in the ACC, a brain region heavily involved in mood regulation (56), following light therapy, may provide a means to improve the efficacy of this treatment. For example: [^{11}C]DASB PET could be similarly applied to determine what aspects (i.e., light color, duration, intensity, time of day, etc.) of light exposure best reduce 5-HTT BP_{ND} in the ACC to optimize this treatment.

One limitation of the present study is that it may have been underpowered to detect changes in 5-HTT BP_{ND} in regions other than the ACC, such as the ventral striatum and hippocampus which had similar magnitudes of change but greater variability of such change. Second, while our cutoff between winter and fall was based on standardized definitions of season, it is possible that the true cutoff at which 5-HTT BP_{ND} in the ACC decreases after light therapy might be earlier, as a cutoff of November 27 would have yielded similar results (magnitude −12.81%, repeated-measures ANOVA, $F_{1,11} = 7.34$, $P = 0.02$). Third, we chose to examine the effect of light therapy in healthy volunteers; thus, the extent to which these findings are generalizable to a clinical population of individuals with SAD is unclear. Another challenge in studying healthy volunteers is that they would be expected to score low on measures of depressed mood and energy both prior to and after light therapy. This floor effect may have limited our ability to detect significant correlations between 5-HTT BP_{ND} and symptom-related scales.

We studied healthy individuals in the fall and winter as the primary aim of this study was to evaluate the potential of 5-HTT BP_{ND} as a biomarker for light exposure to develop prevention strategies for new-onset SAD. Nevertheless, these results suggest several future directions: one future direction should examine the effect of light therapy on 5-HTT BP_{ND} in individuals with subsyndromal or full-syndrome SAD to determine whether there would

be a greater level of response. Another interesting future direction would be to assess the effect of light therapy on 5-HTT BP_{ND} in the spring and summer to further characterize the seasonal variation in response.

In summary, this is the first study to examine the effects of light therapy upon 5-HTT BP_{ND} in the living human brain. The main finding is that 5-HTT BP_{ND} in the ACC was significantly reduced after light therapy relative to placebo treatment in healthy individuals during the winter months. These results provide evidence of a relationship between 5-HTT binding in the ACC and light therapy and identify, for the first time, a central biomarker associated with the therapeutic intervention of light therapy. As such, this central biomarker represents a new approach by which, in the future, different candidate light therapy strategies could be screened with the best-performing method upon reducing 5-HTT BP_{ND} in the ACC being advanced to clinical trial for preventing SAD.

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Significant outcomes

- Serotonin transporter binding was significantly reduced in the anterior cingulate cortex (ACC) of healthy individuals following light therapy relative to placebo during the winter months.
- First evidence of the involvement of the serotonin transporter in the ACC, a brain region with a known role in antidepressant response, in the therapeutic effects of light therapy.
- Identification of a central biomarker that could be applied in the future to assess the effect of modifications of light therapy (i.e., modifications that lead to greater effect on the biomarker could be selected for further investigation).

Limitations

- Possibly underpowered to detect lesser changes in serotonin transporter binding in regions other than the anterior cingulate cortex (ACC) and prefrontal cortex (PFC).
- Healthy volunteers were studied which was advantageous for evaluating light therapy as a preventative strategy. However, this was not studied in seasonal affective disorder.
- Detection of significant correlations between change in symptom-related scales and reduced serotonin transporter binding may have been limited by a floor effect as would be expected when studying healthy volunteers.

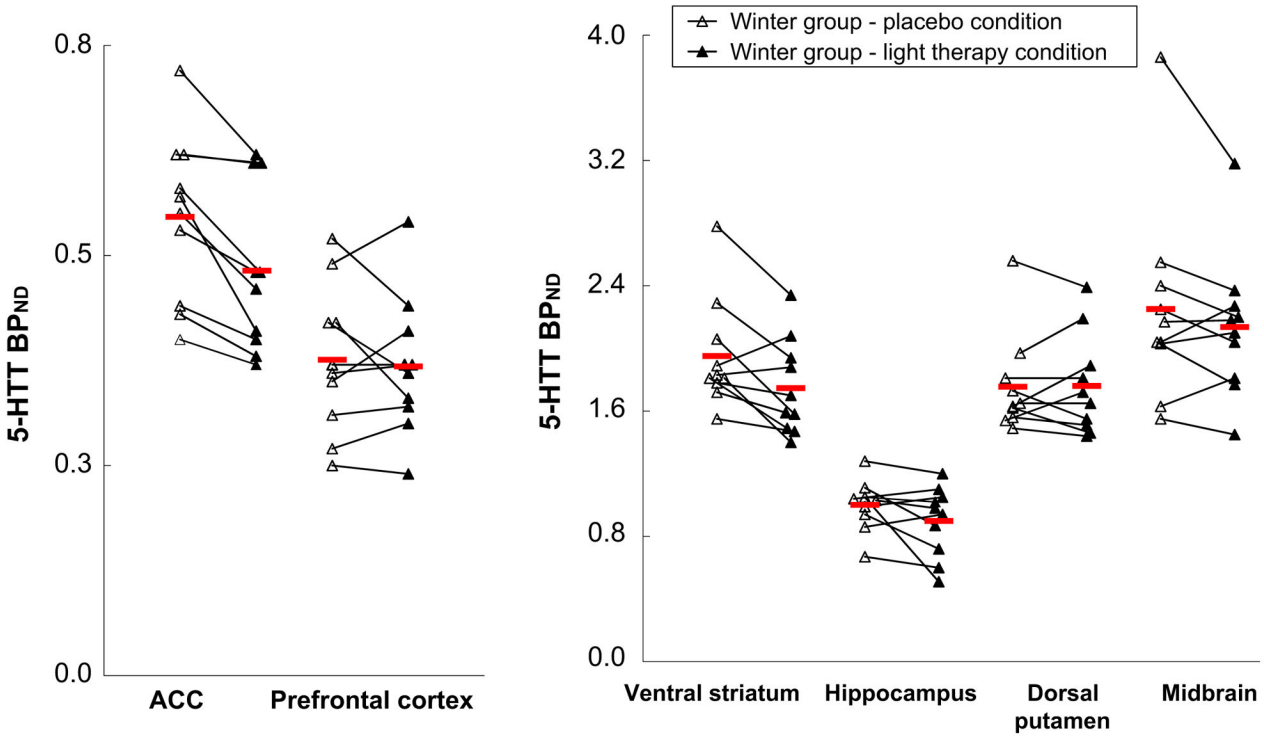

Fig. 1.

Serotonin transporter binding potential (5-HTT BP_{ND}) measured across conditions in six brain regions of interest (ROIs) during the winter ($n = 10$). Open (placebo) and closed (light therapy) triangles represent individual subject 5-HTT BP_{ND} values for each condition, and red bars represent the group mean. ACC refers to anterior cingulate cortex. 5-HTT BP_{ND} was significantly decreased in the ACC of healthy individuals following light therapy relative to placebo. Trend-level reductions in 5-HTT BP_{ND} were also observed in the ventral striatum and hippocampus. Error bars were omitted for clarity.

Table 1

Group differences in brain 5-HTT BP_{ND} values in healthy subjects undergoing positron emission tomography in winter ($n = 10$) and fall ($n = 9$) following light and placebo

	Winter					Fall				
Brain region	**Mean % change***	**Mean difference† (SD)**	**Effect size‡**	**t_9**	***P*-value§**	**Mean % change***	**Mean difference† (SD)**	**Effect size‡**	**t_8**	***P*-value§**
Anterior cingulate cortex	−12.0%	−0.064 (0.048)				1.2%	0.013 (0.093)	0.14	−0.43	0.68
Prefrontal cortex¶	−1.1%	−0.008 (0.053)	0.15	0.48	0.64	6.1%	0.017 (0.035)	0.48	−1.44	0.19
Ventral striatum	−9.9%	−0.205 (0.227)	0.90	2.85	0.02	−2.4%	−0.086 (0.246)	0.35	1.05	0.33
Dorsal putamen	1.0%	0.005 (0.163)	0.03	−0.10	0.93	5.4%	0.108 (0.251)	0.43	−1.29	0.23
Thalamus	4.0%	0.095 (0.275)	0.40**	−1.79††	0.08††	3.7%	0.082 (0.257)	0.32	−0.96	0.37
Midbrain	−3.6%	−0.115 (0.262)	0.44	1.39	0.20	2.3%	−0.032 (0.452)	0.07	0.21	0.84
Hippocampus	−10.0%	−0.103 (0.189)	0.55	1.73	0.12	−3.4%	−0.036 (0.209)	0.17	0.51	0.62

5-HTT BP_{ND}, serotonin transporter binding potential (non-displaceable); dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex.

*Mean % change calculated as: (Light – Placebo)/Light.

†Mean difference calculated as: Light – Placebo.

‡Cohen's *d*.

§Paired, two-tailed *t*-test, uncorrected *P*-value shown.

¶Similar results observed in sub-regions of the PFC (dlPFC, vlPFC, mPFC and OFC).

**Calculated as: Wilcoxon signed-ranks test statistic/Number of observations.

††Non-parametric Wilcoxon signed-ranks test.

Table 2

Group differences in sleep parameters in healthy subjects undergoing positron emission tomography in winter ($n = 10$) and fall ($n = 9$) following light and placebo

	Winter, Mean (SD)				Fall, Mean (SD)			
Sleep parameter	**Light**	**Placebo**	t_9	***P*-value***	**Light**	**Placebo**	t_8	***P*-value***
Bed time†	23:42:00 (1:36:00)	23:31:00 (1:17:00)	−0.48	0.65	23:39:00 (1:07:00)	23:12:00 (1:00:00)	−1.16	0.28
Wake-up time†	05:55:20 (0:54:00)	05:46:05 (0:48:00)	−0.55	0.59	05:29:57 (1:00:00)	05:12:11 (0:39:00)	−1.13	0.29
Sleep latency (mm:ss)	5:11 (3:34)	6:33 (7:37)	0.51	0.62	1:37 (1:36)	3:42 (3:57)	2.02	0.08
Sleep duration (h:mm:ss)	5:19:32 (0:52:00)	5:25:00 (0:42:00)	0.41	0.69	5:13:00 (0:54:00)	5:20:00 (1:12:00)	0.69	0.51
Awakening (*n*)	11.57 (3.49)	12.29 (4.93)	0.48	0.64	9.86 (2.28)	8.68 (1.99)	−1.18	0.27
Sleep efficacy (%)	86.44 (5.01)	87.00 (3.45)	0.44	0.67	89.70 (3.02)	89.00 (3.57)	−0.65	0.53

*Paired, two-tailed *t*-test, uncorrected *P*-value shown.

†24-hour time notation.