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ORIGINAL INVESTIGATION

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Summer and SERT: Effect of daily sunshine hours on *SLC6A4* promoter methylation in seasonal affective disorder

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ABSTRACT

Objectives: Knowledge on how sunlight impacts SERT activity *via SLC6A4* promoter methylation in Seasonal Affective Disorder (SAD) remains limited. This study aimed to investigate the effect of daily sunshine duration on *SLC6A4* promoter methylation in 28 patients with SAD and 40 healthy controls (HC).

Methods: Daily sunlight data for Vienna, Austria (mean of 28 days before blood sampling), were obtained from ©GeoSphere Austria. A general linear model analysed *SLC6A4* promoter methylation as the dependent variable, with sunlight hours as the independent variable, and group (SAD, HC), age, sex, and *5-HTTLPR*/rs25531 as covariates. Exploratory analyses examined the effects of sunlight hours and methylation on Beck Depression Inventory (BDI) scores.

Results: Sunlight had a significant effect on *SLC6A4* promoter methylation ($p=0.03$), with more sunlight hours resulting in lower methylation ($r=-0.25$). However, the interaction between sunlight and group was non-significant, suggesting a rather general effect across both groups. Sunlight also influenced BDI scores ($p<0.01$), with fewer sunlight hours leading to higher scores ($r=-0.25$), which aligns with previous research. *SLC6A4* promoter methylation had no significant effect on BDI scores.

Conclusions: Our findings suggest that sunlight influences *SLC6A4* methylation without SAD specificity.

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SLC6A4; serotonin transporter; methylation; seasonal affective disorder; sunshine

Introduction

The relevance of the serotonin transporter (SERT) to the pathophysiology and treatment of psychiatric disorders is well established. Changes to SERT density were shown in depression and anxiety in humans *in vivo*. The SERT is a central target of various psychopharmacologic treatments, first and foremost selective serotonin reuptake inhibitors (Spies et al. 2015).

The SERT gene (*SLC6A4*) length polymorphism (*5-HTTLPR*) and the associated rs25531 variant are likely among the most studied serotonergic gene variants in the context of psychiatric disorders (Caspi et al. 2003). Epigenetic regulation, such as DNA methylation of the *SLC6A4* gene, was shown to mediate risk for psychiatric conditions. For example, peripheral *SLC6A4* promoter methylation was linked to depression (Kim et al. 2013; Booij et al. 2015; Iga et al. 2016; Schiele et al. 2019) as well as related structural (Dannlowski et al. 2014; Booij et al. 2015; Won et al. 2016) and functional (Frodl et al. 2015; Ismaylova et al. 2018; Schneider et al. 2018) imaging endophenotypes. In addition, methylation status may be related to treatment outcomes (Domschke et al. 2014; Okada et al. 2014; Schiele et al. 2021). Various stress-related risk factors for affective disorders were shown to result in altered *SLC6A4* promoter methylation, with both increases (Zhao et al. 2013; Booij et al. 2015; Duman and Canli 2015) and decreases reported (Devlin et al. 2010; Alasaari et al. 2012). Thus, changes to *SLC6A4* promoter methylation may serve as an intermediate between disease risk and the clinical manifestation of psychiatric illnesses.

The serotonergic system is susceptible to season (Matheson et al. 2015) and light (Spindelegger et al. 2012; Harrison et al. 2015; Tyrer et al. 2016). Cerebral

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SERT protein levels are higher in fall/winter and lower in spring/summer (Ruhé et al. 2009), and show a negative association with sunshine levels (Praschak-Rieder et al. 2008). Dysregulation of seasonal fluctuations in SERT expression may underlie Seasonal Affective Disorder (SAD) (Mc Mahon et al. 2016), a condition characterised by depressive symptoms in fall/winter and remission in spring/summer, where both season and light act as risk factors and directly impact pathophysiology (Mersch et al. 1999). In fact, a reduction in brain SERT levels was shown after bright light therapy (BLT), the gold-standard treatment for SAD (Harrison et al. 2015; Tyrer et al. 2016), underlining the SERT's pathophysiologic relevance.

Various environmental factors impact epigenetic processes within the brain (Lim 2021). However, little is known about the effect of season on epigenetic regulation of the serotonin system in general, and the SERT in particular. In theory, alterations in methylation mediated by seasonal and environmental factors might underlie the changes in SERT expression observed in SAD. Of seasonal variables, temperature (Bind et al. 2014; Xu et al. 2021) and light exposure (Da Silva Melo et al. 2015; Vandiver et al. 2015) were shown to influence methylation patterns in the human genome. However, the influence of these environmental factors on *SLC6A4* promoter methylation has yet to be elucidated.

Here, we aimed to investigate this relationship by assessing the impact of meteorologic measures, gleaned from regional assessments, on peripheral *SLC6A4* promoter methylation in a cohort of patients with SAD as well as healthy controls (HC). We analysed methylation within four *SLC6A4* promoter CpG sites previously linked to affective disorders and their treatment (Domschke et al. 2014).

Material and methods

Study design

Methylation data from 28 (18/10 f/m) patients diagnosed with SAD and 40 HC (23/17 f/m) were analysed ($n = 68$). Data were gleaned from a previously published placebo-controlled study using positron emission tomography (PET) to investigate the effect of BLT on MAO-A density in the brain across the seasons (Spies et al. 2018). This previous study encompassed a screening visit, a structural magnetic resonance imaging (MRI) scan, three positron emission tomography (PET) scans (PET1, before BLT/placebo-treatment in autumn or winter; PET2, after BLT/placebo-treatment in autumn/winter; and PET3, after BLT/placebo-treatment in spring or summer) as well as a follow-up visit. For the analyses at hand, no imaging data (i.e. PET or MRI data) was used. Blood draw for methylation analysis was either conducted before PET1 or PET2 in autumn or winter (September to February) or before PET3 in spring or summer (March to August). Beck Depression Inventory (BDI) (Beck et al. 1961) scores were assessed in the same season as the blood sample was taken. If the BDI score was obtained in a different season, the patient was excluded from BDI-related analyses. The study was conducted in accordance with the Declaration of Helsinki, taking all current revisions and the good scientific practice guidelines of the Medical University of Vienna into account. The protocol was approved by the ethics committee of the Medical University of Vienna (EC No. 1681/2016) and registered at clinicaltrials.gov (NCT02582398).

Participants

Patients with SAD were enrolled at the outpatient clinic of the Department of Psychiatry and Psychotherapy at the Medical University of Vienna. HC were recruited *via* dedicated message boards at the Medical University of Vienna. The Structured Clinical Interview for DSM-4 Axis I disorders (SCID-I) (First et al. 2002) as well as the Seasonal Pattern Assessment Questionnaire (SPAQ) (Raheja et al. 1996) were performed in all patients to confirm the diagnosis of unipolar winter-type SAD and to exclude any other type of psychiatric condition. The SCID-I and the SPAQ were used in HC to exclude psychiatric diagnoses, particularly SAD. Participants were excluded if they were undergoing current psychopharmacological treatment or had received such treatment within six months prior to enrolment. Additional exclusion criteria included severe somatic or neurologic comorbidities, current smoking, drug abuse, pregnancy, or lactation. A trained physician assessed potential contraindications during the initial visit through a review of medical history, routine laboratory tests (blood and urine), electrocardiography, and a physical examination. All participants provided written informed consent and received financial compensation for their participation. An overview of subject characteristics including demographic information can be found in Table 1.

Methylation analysis and SLC6A4 genotyping

DNA methylation analysis was performed at the Department of Psychiatry and Psychotherapy at the University of Freiburg, Faculty of Medicine, Germany *via* direct sequencing of bisulfite-converted DNA. Methylation levels at 4 CpG sites (CpG1 = 30,236,072; CpG2 = 30,236,084; CpG3 = 30,236,089; CpG4 = 30,236,091)

Table 1. Demographic and clinical characteristics of the study sample.

	HC		SAD	
	Mean	**SD**	**Mean**	**SD**
Age	34,35	9,96	32,86	9,55
BDI	1,33	2,26	11,92	7,86
Avg. Meth.	4,64	0,97	4,63	0,99
Avg. Sun	5,74	2,39	3,78	2,59
Avg. Temp.	15,37	6,98	9,80	6,89

Sex	23 (Female)		17 (Male)	18 (Female)		10 (Male)
SERT-LPR	10 (S1+S1)	16 (S1+LA)	14 (LA+LA)	8 (S1+S1)	14 (S1+LA)	6 (LA+LA)

The table shows the demographic and clinical characteristics of healthy controls (HC) and patients with Seasonal Affective Disorder (SAD). Values for age, Beck Depression Inventory (BDI) scores, average *SLC6A4* promoter methylation (Avg. Meth.), average daily sunlight hours (Avg. Sun), and average temperature (Avg. Temp.) are reported as means with standard deviations (SD). Sex distribution is displayed as the number of female and male participants per group. Genotypic distribution of the serotonin transporter gene-linked polymorphic region (SERT-LPR) is presented for each group, categorised into S1+S1, S1+LA, and LA+LA.

(Domschke et al. 2014) located in a 20 bp amplicon in the *SLC6A4* promoter (chromosome 17: 30,236,072–30,236,091; GRCh38.p2 Primary Assembly, UCSC Genome Browser) were analysed in every individual sample by pyrosequencing (PyroMark Q96 ID, Qiagen) as described previously (Ziegler et al. 2016).

All subjects were genotyped for the *5-HTTLPR*, as the short allele of *5-HTTLPR* has been associated with depression (Collier et al. 1996), SAD (Rosenthal et al. 1998) and seasonality (Johansson et al. 2003). Additionally, genotyping included the *SLC6A4* single nucleotide polymorphism (SNP) rs25531, which modifies the long allele (L) of *5-HTTLPR*. The rs25531 polymorphism differentiates between the LA variant (which retains high SERT expression) and the LG variant (which reduces SERT expression and is functionally similar to the short allele, S) (Kraft et al. 2005; Hu et al. 2006). Thus, in this study, S1 refers to both the short allele (S) and the LG variant of the long allele, as both are functionally similar in their effects on SERT expression. Genotypes were categorised into three groups: S1+S1, S1+LA, and LA+LA. Genotyping was performed at the Department of Psychiatry, Psychotherapy and Psychosomatics of the University of Halle, Germany, as outlined in Baldinger et al. (2015).

Assessment of meteorological data

Datasets on daily sunlight hours and temperature for the 28 days preceding blood sampling were obtained for each participant from two separate meteorological measurement stations in Vienna, Austria. These data were sourced from ©GeoSphere Austria (https://data.hub.geosphere.at). The first station is located in the outskirts of Vienna ('Hohe Warte'), while the second is situated in the city-centre ('Innere Stadt'). For each individual, the meteorological data from both stations were averaged. These averaged values were then utilised for subsequent statistical analyses. Due to the high correlation ($r=0.86$) between average sunlight hours and average temperature, only sunlight hours were considered in the final statistical procedures.

Statistical analysis

Statistical tests were performed using SPSS version 28 for Windows (SPSS Inc., Chicago, IL, USA).

Analyses of SLC6A4 promoter methylation

Average *SLC6A4* promoter methylation was described as the average methylation of all pre-defined CpG sites (CpG 1-4) and could be obtained from 40 (23/17 females/males) HC (mean age 34.35 ±SD 9.96 years) and 28 (18/10 females/males) patients with SAD (mean age 32.86±SD 9.55 years). In a first step, average CpG methylation was tested for normality using the Shapiro-Wilk test ($p=0.54$; normally distributed). A general linear model (GLM) was then applied to investigate the relationship between average CpG methylation (dependent variable) and average sunlight hours (independent variable). The model also included the covariates group (patients with SAD vs. HC), *5-HTTLPR*/rs25531 genotype, sex, and age. All continuous variables (i.e. average CpG methylation, age, average sunlight hours) were z-scored.

Then, a second GLM was calculated in an exploratory manner with the interaction effect between group and average sunlight hours as an additional covariate to investigate whether there is a pathophysiologically relevant effect of SAD. Post hoc analyses were performed using Spearman's correlation.

Beck depression inventory

BDI scores were collected and incorporated into the study to quantify the extent of depressive symptoms and to explore the potential relationship between this

clinical parameter, sunlight exposure, and *SLC6A4* promoter methylation.

BDI scores were available for 22 (13/9 females/males) patients with SAD (mean age 31.41 ± SD 9.67 years) and 28 (16/12 females/males) HC (mean age 33.18 ± SD 9.9 years). To investigate the relationship between the BDI scores (dependent variable) and average sunlight hours (independent variable) in patients with SAD, a GLM with the covariates *5-HTTLPR*/rs25531 genotype, sex and age was calculated. The same model was applied using the BDI scores of HC. Of note, the analysis was split due to the naturally high difference in BDI between patients with SAD and HC.

In a second BDI-related GLM, the potential influence of *SLC6A4* promoter methylation (independent variable) on BDI scores (dependent variable) was calculated in patients with SAD, using *5-HTTLPR*/rs25531 genotype, sex and age as covariates. Again, the model was repeated using the BDI scores of HC. In both models, all continuous variables (i.e. BDI scores, average CpG methylation, age, average sunlight hours) were z-scored. The reduced sample size for this model can be attributed to the criterium limiting participants to those whose BDI scores were assessed in temporal proximity (e.g. in the same season) with the blood draws for methylation analysis. A correction for the number of subject groups (SAD patients and HC) was performed *via* Bonferroni correction, significance was set at $p < 0.05$.

With our main model and a total sample size of 68 subjects, we were able to detect effect sizes of Cohen's $f = 0.42$ ($\alpha = 0.05$, two-tailed, power = 0.8). The sample size estimation was performed using G*Power 3.1.9.7. While this corresponds to a relatively large effect size, it reflects the limitations imposed by the available data and is consistent with the obtained p-value of 0.029.

Results

Analyses of SLC6A4 promoter methylation

As shown in Figure 1, the main model revealed a significant influence of average sunlight hours on average *SLC6A4* promoter methylation ($p = 0.03$). This could be confirmed by post hoc Spearman's correlation analysis ($r = -0.25$), indicating that more sunlight hours result in lower methylation levels. Regarding the covariates included in the model, no significant effect of group (patients with SAD vs. HC), *5-HTTLPR*/rs25531 genotype, sex, or age was found.

Adding the interaction between average sunlight and group as a potential covariate to the model (exploratory GLM model) resulted in a non-significant outcome between this factor and average sunlight hours ($p = 0.7$).

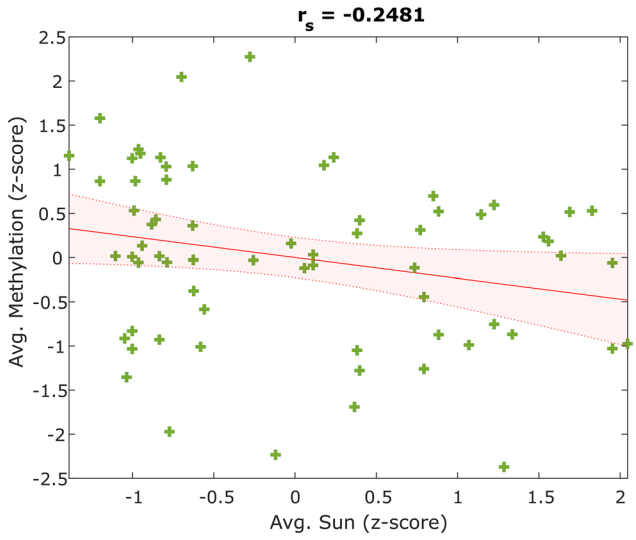

Figure 1. Relationship between average sunlight hours and *SLC6A4* promoter methylation: the plot illustrates the significant influence of sunlight hours per day, averaged from a time frame of 28 days prior to blood sampling, on average *SLC6A4* promoter methylation ($p_{uncorr.} = 0.03$). Values are z-scored. The main model shows a negative correlation, confirmed by post hoc Spearman's correlation analysis ($r = 0.25$), indicating that increased sunlight hours are associated with lower methylation levels of the *SLC6A4* promoter.

Beck depression inventory

The exploratory analysis investigating the potential impact of average sunlight hours on BDI scores in patients with SAD yielded a significant finding; as demonstrated in Figure 2, an increase in average sunlight hours resulted in a reduction in BDI scores ($p < 0.01$). This could be confirmed by post hoc Spearman's correlation analysis ($r = -0.41$). No significant relationship between average sunlight hours and BDI scores was observed in HC. Although the model indicated a significant effect of gender on BDI scores, with women ($p_{uncorr.} = 0.04$) showing higher BDI scores than men within the subpopulation of patients with SAD, this finding did not remain significant after correction for multiple comparisons. Therefore, this result should be interpreted with caution and may not represent a true effect. Additionally, the model investigating the influence of average *SLC6A4* promoter methylation on BDI scores yielded no significant results in neither the SAD nor the HC group.

Discussion

The study at hand explored the effect of average sunlight hours per day on *SLC6A4* promoter methylation in a cohort consisting of patients with SAD and HC. The analysis revealed that sunlight exposure significantly influenced *SLC6A4* promoter methylation,

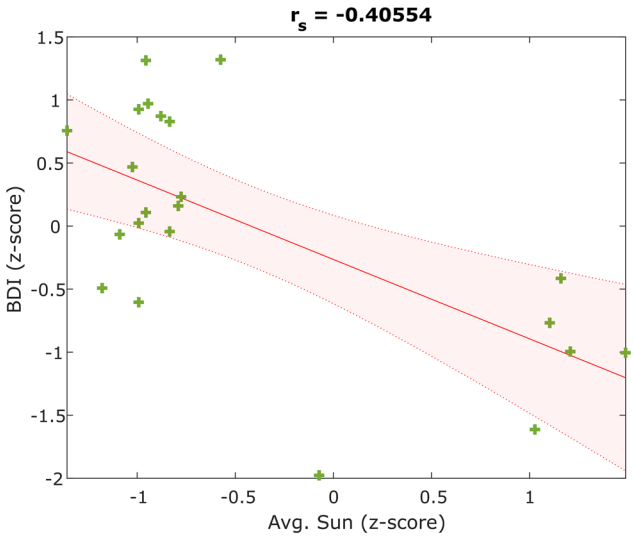

Figure 2. Influence of average sunlight hours per day on BDI scores in patients with SAD: the plot shows the significant effect of average sunlight hours per day, averaged from a time frame of 28 days prior to blood sampling, on BDI scores in patients with SAD ($p_{uncorr.} < 0.01$). Values are z-scored. An increase in average sunlight hours corresponds to a reduction in BDI scores, as confirmed by post hoc Spearman's correlation analysis ($r = 0.41$).

linking increased sunlight hours to reduced methylation levels. The remaining covariates included in the main model (i.e. health status, *5-HTTLPR*/rs25531 genotype, sex and age) did not show a significant effect on methylation. Our exploratory models examining the effect of average sunlight hours and *SLC6A4* promoter methylation on BDI scores indicated that average sunlight hours significantly influenced the BDI scores of patients with SAD, with more sunlight hours resulting in lower scores. Furthermore, women (compared to men) exhibited elevated BDI scores, however this finding did not survive correction for multiple comparisons. *SLC6A4* promoter methylation did not exert a significant impact on BDI scores. The other factors assessed did not significantly affect BDI scores either.

Analyses of SLC6A4 promoter methylation

Epigenetic modifications influence how the DNA sequence is read to orchestrate protein synthesis. One form of epigenetic regulation is DNA methylation, with methyl groups attaching to specific sites on the DNA strand to regulate accessibility for RNA polymerases and thus gene activity. At specific CpG sites, elevated methylation leads to reduced transcriptional activity and thus lower protein levels (Lee et al. 2005). The gene *SLC6A4* codes for the SERT, whose relevance for SAD has been shown in numerous studies (Willeit et al. 2008; Ruhé et al. 2009; Mc Mahon et al. 2016; Tyrer et al. 2016; Mc Mahon et al. 2018). These investigations consistently suggest a diminished downregulation of SERT activity (i.e. elevated SERT activity) in patients with SAD during the winter months, resulting in increased serotonin reuptake and consequently lower serotonin availability. Nevertheless, seasonally relevant epigenetic mechanisms potentially influencing SERT activity have not yet been sufficiently investigated. DNA methylation per se is known to be influenced by meteorologic and seasonal factors (Bind et al. 2014; Ricceri et al. 2014; Handschuh et al. 2023), including sunlight exposure (Aslibekyan et al. 2014; Nair-Shalliker et al. 2014). Given the shown lack of downregulation of SERT density in patients with SAD during winter and the established impact of methylation on protein expression, it remains plausible to hypothesise that *SLC6A4* promoter methylation is influenced by daily sunlight duration. This would suggest a pattern of decreased methylation in winter, when sunlight hours are reduced, potentially leading to increased SERT expression and decreased serotonin availability, which may contribute to the development of winter-type depression. However, our findings indicated a different trend, suggesting that increased sunlight hours were associated with lower *SLC6A4* promoter methylation. This suggests that the relationship may be more nuanced, potentially influenced by additional factors beyond sunlight exposure alone, warranting further investigation.

This trend is in line with previously published findings, pointing towards reduced DNA methylation of certain genes after sun exposure when analysing methylation in circulating peripheral blood cells, such as lymphocytes (Nair-Shalliker et al. 2014).

As described above, SERT is a crucial component in SAD pathophysiology, with higher SERT density during winter, resulting in worse clinical outcomes. Theoretically, lower *SLC6A4* promoter methylation levels could lead to increased transcriptional activity and protein synthesis, resulting in higher SERT density. Given that peripheral *SLC6A4* promoter methylation was higher (rather than lower) during periods of fewer sunlight hours per day (i.e. during autumn and winter), three theoretical conclusions can be drawn: First, the relationship between peripheral DNA methylation levels and brain SERT density, as well as neurotransmitter levels in SAD, may be more complex than initially assumed, suggesting that peripheral *SLC6A4* promoter methylation levels may not directly predict these variables in a straightforward or reliable manner. Second, it can be hypothesised that lower peripheral *SLC6A4*

promoter methylation in response to more sunlight hours per day should be seen as a general effect of sunlight exposure found in various genes, as evidenced by previous methylation studies investigating the impact of sunlight on peripheral gene methylation (Aslibekyan et al. 2014; Nair-Shalliker et al. 2014). Third, other biological mechanisms beyond sunlight exposure may be influencing *SLC6A4* promoter methylation, potentially overshadowing the direct effects of sunlight alone, suggesting that the relationship between sunlight hours and methylation may be part of a more complex network of regulatory processes, requiring further investigation to disentangle the relative contributions of these variables.

Returning to the potential effects of sunlight on *SLC6A4* methylation, one key mechanism involves the serotonergic system, as light exposure modulates serotonin synthesis and metabolism, which in turn can impact epigenetic regulation. Additionally, the melatonin-serotonin axis is closely linked to seasonal light variation, and alterations in this pathway may contribute to changes in methylation patterns: Serotonin plays a crucial role in the regulation of circadian rhythms, particularly within the suprachiasmatic nucleus (SCN), where it modulates the sensitivity of the circadian system to light (Morin 1999). Another potential mechanism is the role of vitamin D, which is synthesised in response to sunlight and has been implicated in epigenetic modifications, including DNA methylation (Fetahu et al. 2014). Furthermore, seasonal fluctuations in stress hormone levels, such as cortisol, could mediate the effects of sunlight on *SLC6A4* methylation. While SAD has been discussed as a potential hypocortisolemic condition (Agustini et al. 2019), findings on Hypothalamic-Pituitary-Adrenal (HPA) axis function remain inconclusive. Some studies suggest that patients with SAD exhibit an attenuated Cortisol Awakening Response (CAR) in winter (Thorn et al. 2011), while others report normal suppression in the Dexamethasone Suppression Test (DST) (James et al. 1986). Given that sunlight exposure influences HPA axis regulation, with reduced daylight potentially contributing to altered cortisol rhythms, seasonal variations in cortisol levels may, in turn, impact *SLC6A4* methylation. Since stress-related epigenetic modifications of *SLC6A4* have been reported (Provenzi et al. 2016), it is plausible that HPA axis dysregulation in SAD partially mediates the observed methylation changes, providing a possible link between environmental light conditions and serotonergic functioning.

When examining the influence of peripheral DNA methylation on transcriptional processes related to *SLC6A4*, Wankerl et al. found that variations in SERT mRNA levels are unlikely to be influenced by DNA methylation patterns within the SERT gene (Wankerl et al. 2014). Another study published by Okada et al. reported that the methylation state of an *SLC6A4* CpG island (a gene region with elevated density of CpG dinucleotides) did not distinguish unmedicated patients diagnosed with major depression from either medicated patients or healthy participants (Okada et al. 2014), further questioning the relevance of average peripheral *SLC6A4* DNA methylation on transcription regulation. Conversely, Ouellet-Morin et al. found that increased *SLC6A4* DNA methylation was associated with bullying victimisation when comparing the methylation state of bullied twins to the one of their non-bullied co-twins, supporting the hypothesis that childhood stress influences *SLC6A4* DNA methylation, thus linking methylation patterns to mental health conditions (Ouellet-Morin et al. 2013).

Mixed results in terms of risk factors for affective disorders modifying *SLC6A4* DNA methylation – with studies linking these risk factors to either higher (Zhao et al. 2013; Booij et al. 2015; Duman and Canli 2015) or lower (Devlin et al. 2010; Alasaari et al. 2012) methylation levels – also emphasise the complex interplay of *SLC6A4* DNA methylation, SERT expression, serotonin availability and environmental factors. As systematically reviewed by Provenzi et al., *SLC6A4* DNA methylation has been investigated in relation to various prenatal and postnatal adverse exposures, including maternal depression during pregnancy, perinatal and environmental stress as well as childhood trauma (Provenzi et al. 2016). The authors found that *SLC6A4* might be seen as a relevant biomarker of early adversity exposures, with epigenetic mechanisms at this gene playing a critical role in programming.

Despite these efforts, establishing a causal relationship between *SLC6A4* DNA methylation and depression is challenging due to several factors inherent in the design and execution of human studies. First, the studies conducted so far employ different study designs, making direct comparisons difficult. Also, there is great variability in the specific methylation sites being analysed, and further epigenetic mechanisms such as hydroxymethylation or histone modifications – potentially also influencing SERT expression – were not considered so far (Ell et al. 2024). Additionally, study populations are rarely comparable regarding disease characteristics, medication use, age, and geographical location, further complicating the ability to draw definitive conclusions. Moreover, differences in sample size, statistical power, and the presence of confounding variables such as genetic background as well as pre- and postnatal stress

and lifestyle factors contribute to the complexity (Schraut et al. 2014). The dynamic nature of DNA methylation, influenced by both genetic and environmental factors over time, adds another layer of difficulty in establishing a direct causal link between *SLC6A4* DNA methylation and depression. Furthermore, as discussed earlier, we cannot be certain that *SLC6A4* promoter methylation data collected from peripheral blood samples accurately represents SERT density in the brain. *In vivo* imaging studies with clinical and healthy cohorts using, e.g. PET are needed to fill this gap in knowledge and provide a more accurate understanding of the relationship between peripheral *SLC6A4* DNA methylation, SERT density and clinical outcomes. Nevertheless, the study at hand is the first to analyse *SLC6A4* promoter methylation in SAD while considering meteorological data and the influence of sunlight on methylation dynamics. However, two limitations should be noted at this point: First, while we retrieved daily meteorological data for the 28 days prior to blood sampling, we did not monitor the exact locations of participants during this period, only that their primary residence was in Vienna. Second, in a limited subset of individuals, blood sampling was conducted before PET3, which occurred after treatment with either BLT or placebo. Consequently, we cannot entirely rule out potential effects of BLT on SERT methylation in those participants. Despite these limitations, the present approach is crucial for future investigations, as it underscores the potential impact of environmental factors on epigenetic modifications, offering a more comprehensive understanding of SAD. Such studies are relevant for clinical investigations in psychiatry because they can inform more targeted and effective treatments, considering both epigenetic and environmental influences on mental health.

Beck depression inventory

BDI scores were used to assess the severity of depressive symptoms, allowing for the exploration of the potential relationship between clinical characteristics, sunlight exposure, and *SLC6A4* promoter methylation. Our exploratory models examining the effect of average sunlight hours and *SLC6A4* promoter methylation on BDI scores revealed several key findings. Average sunshine hours significantly influenced BDI scores in patients with SAD, with increased sunshine hours leading to lower BDI scores. This is consistent with previous observations that sunlight exposure can alleviate depressive symptoms in SAD, possibly through its role in serotonin (Lambert et al. 2002) and vitamin D (Milaneschi et al. 2014; Akpınar and Karadağ 2022) synthesis, as well as in regulating circadian rhythms (Boivin et al. 1996) by exerting positive effects on the suprachiasmatic nuclei (Bedrosian and Nelson 2017). Women had higher BDI scores than men in our study, although this finding lacked significance after correction for multiple comparisons. The higher prevalence of depression in women (Hyde and Mezulis 2020) could be traced back to several factors, including hormonal fluctuations (Kundakovic and Rocks 2022), differential psychosocial stress management (Dong et al. 2022) and gender-specific coping mechanisms (Graves et al. 2021). *SLC6A4* promoter methylation had no significant effect on BDI scores, nor did any of the other factors assessed. This suggests that while epigenetic modifications of *SLC6A4* may play a role in stress responses (Bakusic et al. 2020), their direct influence on depressive symptoms in SAD requires further investigation. Future studies should explore the interaction between (epi)genetic predisposition, environmental factors, and gender differences to better understand the complex mechanisms underlying SAD.

Conclusion

The study at hand aimed to investigate the potential impact of average sunlight hours on *SLC6A4* promoter methylation and SAD symptomatology. Our findings demonstrated that increased sunlight exposure was significantly associated with reduced *SLC6A4* promoter methylation, suggesting an epigenetic response to seasonal changes of sunlight hours. Contrary to presumed expectations, *SLC6A4* promoter methylation increased with fewer sunlight hours per day, questioning the importance of *SLC6A4* DNA methylation in SAD. Since methylation was influenced solely by sunlight hours, without a significant interaction with mental health status, the effect appears general rather than specifically relevant to SAD. Average sunlight hours were found to significantly influence BDI scores in SAD, with more sunlight leading to lower BDI scores. This supports existing observations that sunlight exposure can mitigate depressive symptoms. The lack of a significant impact of *SLC6A4* promoter methylation on BDI scores and other assessed factors highlights the complexity of the interplay between genetic, epigenetic, and environmental influences on SAD. These results indicate that the connection between sunlight exposure and methylation may be influenced by a more intricate set of regulatory mechanisms.

The relationship between methylation and protein expression may be non-linear. Further research using

in vivo imaging techniques, such as PET is necessary to better understand the relationship between peripheral DNA methylation, brain SERT density, and clinical outcomes. This study is pioneering in its examination of *SLC6A4* promoter methylation in SAD while considering sunlight exposure. This approach underscores the importance of environmental factors in epigenetic modifications and their potential role in psychiatric conditions.

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Patricia A. Handschuh: Conceptualisation, Data Curation, Investigation, Methodology, Visualisation, Writing: Original Draft; Matej Murgaš: Conceptualisation, Formal Analysis, Methodology, Validation, Visualisation, Writing – review & editing; Dietmar Winkler: Funding acquisition, Writing – review & editing; Edda Winkler-Pjrek: Writing – review & editing; Annette M. Hartmann: Data curation, Investigation, Writing – review & editing; Katharina Domschke: Data curation, Investigation, Resources, Writing – review & editing; Pia Baldinger-Melich: Investigation, Writing – review & editing; Dan Rujescu: Resources, Supervision, Writing – review & editing; Rupert Lanzenberger: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing; Marie Spies: Conceptualisation, Data Curation, Investigation, Methodology, Supervision, Writing – Original Draft.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (GPT-4-turbo, September 2024) in order to improve language accuracy. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Disclosure statement

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References

Agustini B, Bocharova M, Walker AJ, Berk M, Young AH, Juruena MF. 2019. Has the sun set for seasonal affective disorder and HPA axis studies? A systematic review and future prospects. J Affect Disord. 256:584–593. doi:10.1016/j.jad.2019.06.060.

Akpınar Ş, Karadağ MG. 2022. Is vitamin D important in anxiety or depression? What is the truth? Curr Nutr Rep. 11(4):675–681. doi:10.1007/s13668-022-00441-0.

Alasaari JS, Lagus M, Ollila HM, Toivola A, Kivimäki M, Vahtera J, Kronholm E, Härmä M, Puttonen S, Paunio T. 2012. Environmental stress affects DNA methylation of a CpG rich promoter region of serotonin transporter gene in a nurse cohort. PLoS One. 7(9):e45813. doi:10.1371/journal.pone.0045813.

Aslibekyan S, Dashti HS, Tanaka T, Sha J, Ferrucci L, Zhi D, Bandinelli S, Borecki IB, Absher DM, Arnett DK, et al. 2014. PRKCZ methylation is associated with sunlight exposure in a North American but not a mediterranean population. Chronobiol Int. 31(9):1034–1040. doi:10.3109/07420528.2014.944266.

Bakusic J, Vrieze E, Ghosh M, Bekaert B, Claes S, Godderis L. 2020. Increased methylation of NR3C1 and SLC6A4 is associated with blunted cortisol reactivity to stress in major depression. Neurobiol Stress. 13:100272. doi:10.1016/j.ynstr.2020.100272.

Baldinger P, Kraus C, Rami-Mark C, Gryglewski G, Kranz GS, Haeusler D, Hahn A, Spies M, Wadsak W, Mitterhauser M, et al. 2015. Interaction between 5-HTTLPR and 5-HT1B genotype status enhances cerebral 5-HT1A receptor binding. Neuroimage. 111:505–512. doi:10.1016/j.neuroimage.2015.01.049.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. 1961. An inventory for measuring depression. Arch Gen Psychiatry. 4(6):561–571. doi:10.1001/archpsyc.1961.01710120031004.

Bedrosian TA, Nelson RJ. 2017. Timing of light exposure affects mood and brain circuits. Transl Psychiatry. 7(1):e1017–e1017. doi:10.1038/tp.2016.262.

Bind M-A, Zanobetti A, Gasparrini A, Peters A, Coull B, Baccarelli A, Tarantini L, Koutrakis P, Vokonas P, Schwartz J. 2014. Effects of temperature and relative humidity on DNA methylation.

Epidemiology. 25(4):561–569. doi:10.1097/EDE.0000000000000120.
Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. 1996. Dose-response relationships for resetting of human circadian clock by light. Nature. 379(6565):540–542. doi:10.1038/379540a0.
Booij L, Szyf M, Carballedo A, Frey EM, Morris D, Dymov S, Vaisheva F, Ly V, Fahey C, Meaney J, et al. 2015. DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. PLoS One. 10(3): e0119061. doi:10.1371/journal.pone.0119061.
Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 301(5631):386–389. doi:10.1126/science.1083968.
Collier DA, Stöber G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, et al. 1996. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry. 1(6):453–460.
Da Silva Melo AR, Barroso H, Uchôa De Araújo D, Ruidomar Pereira F, De Oliveira NF. 2015. The influence of sun exposure on the DNA methylation status of MMP9, miR-137, KRT14 and KRT19 genes in human skin. Eur J Dermatol. 25(5):436–443. doi:10.1684/ejd.2015.2598.
Dannlowski U, Kugel H, Redlich R, Halik A, Schneider I, Opel N, Grotegerd D, Schwarte K, Schettler C, Ambrée O, et al. 2014. Serotonin transporter gene methylation is associated with hippocampal gray matter volume. Hum Brain Mapp. 35(11):5356–5367. doi:10.1002/hbm.22555.
Devlin AM, Brain U, Austin J, Oberlander TF. 2010. Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. PLoS One. 5(8):e12201. doi:10.1371/journal.pone.0012201.
Domschke K, Tidow N, Schwarte K, Deckert J, Lesch KP, Arolt V, Zwanzger P, Baune BT. 2014. Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response. Int J Neuropsychopharmacol. 17(8):1167–1176. doi:10.1017/S146114571400039X.
Dong D, Ironside M, Belleau EL, Sun X, Cheng C, Xiong G, Nickerson LD, Wang X, Yao S, Pizzagalli DA. 2022. Sex-specific neural responses to acute psychosocial stress in depression. Transl Psychiatry. 12(1):2. doi:10.1038/s41398-021-01768-y.
Duman EA, Canli T. 2015. Influence of life stress, 5-HTTLPR genotype, and SLC6A4 methylation on gene expression and stress response in healthy caucasian males. Biol Mood Anxiety Disord. 5(1):2. doi:10.1186/s13587-015-0017-x.
Ell MA, Schiele MA, Iovino N, Domschke K. 2024. Epigenetics of fear, anxiety and Stress - focus on histone modifications. Curr Neuropharmacol. 22(5):843–865. doi:10.2174/1570159X21666230322154158.
Fetahu IS, Höbaus J, Kállay E. 2014. Vitamin D and the epigenome. Front Physiol. 5:164. doi:10.3389/fphys.2014.00164.
First MB, Spitzer RL, Gibbon M, Williams J. 2002. Structured clinical interview for DSM-IV-TR Axis I disorders, research version. Biometrics Research, New York State Psychiatric Institute, New York.
Frodl T, Szyf M, Carballedo A, Ly V, Dymov S, Vaisheva F, Morris D, Fahey C, Meaney J, Gill M, et al. 2015. DNA methylation of the serotonin transporter gene (SLC6A4) is associated with brain function involved in processing emotional stimuli. J Psychiatry Neurosci. 40(5):296–305. doi:10.1503/jpn.140180.
Graves BS, Hall ME, Dias-Karch C, Haischer MH, Apter C. 2021. Gender differences in perceived stress and coping among college students. PLoS One. 16(8):e0255634. doi:10.1371/journal.pone.0255634.
Handschuh PA, Murgaš M, Vraka C, Nics L, Hartmann AM, Winkler-Pjrek E, Baldinger-Melich P, Wadsak W, Winkler D, Hacker M, et al. 2023. Effect of MAOA DNA methylation on human in vivo protein expression measured by [11C]harmine positron emission tomography. Int J Neuropsychopharmacol. 26(2):116–124. doi:10.1093/ijnp/pyac085.
Harrison SJ, Tyrer AE, Levitan RD, Xu X, Houle S, Wilson AA, Nobrega JN, Rusjan PM, Meyer JH. 2015. Light therapy and serotonin transporter binding in the anterior cingulate and prefrontal cortex. Acta Psychiatr Scand. 132(5): 379–388. doi:10.1111/acps.12424.
Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, et al. 2006. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet. 78(5):815–826. doi:10.1086/503850.
Hyde JS, Mezulis AH. 2020. Gender differences in depression: biological, affective, cognitive, and sociocultural factors. Harv Rev Psychiatry. 28(1):4–13. doi:10.1097/HRP.0000000000000230.
Iga J, Watanabe SY, Numata S, Umehara H, Nishi A, Kinoshita M, Inoshita M, Shimodera S, Fujita H, Ohmori T. 2016. Association study of polymorphism in the serotonin transporter gene promoter, methylation profiles, and expression in patients with major depressive disorder. Hum Psychopharmacol. 31(3):193–199. doi:10.1002/hup.2527.
Ismaylova E, Lévesque ML, Pomares FB, Szyf M, Nemoda Z, Fahim C, Vitaro F, Brendgen M, Dionne G, Boivin M, et al. 2018. Serotonin transporter promoter methylation in peripheral cells and neural responses to negative stimuli: a study of adolescent monozygotic twins. Transl Psychiatry. 8(1):147. doi:10.1038/s41398-018-0195-6.
James SP, Wehr TA, Sack DA, Parry BL, Rogers S, Rosenthal NE. 1986. The dexamethasone suppression test in seasonal affective disorder. Compr Psychiatry. 27(3):224–226. doi:10.1016/0010-440x(86)90045-3.
Johansson C, Willeit M, Levitan R, Partonen T, Smedh C, Del Favero J, Bel Kacem S, Praschak-Rieder N, Neumeister A, Masellis M, et al. 2003. The serotonin transporter promoter repeat length polymorphism, seasonal affective disorder and seasonality. Psychol Med. 33(5):785–792. doi:10.1017/s0033291703007372.
Kim JM, Stewart R, Kang HJ, Kim SW, Shin IS, Kim HR, Shin MG, Kim JT, Park MS, Cho KH, et al. 2013. A longitudinal study of SLC6A4 DNA promoter methylation and post-stroke depression. J Psychiatr Res. 47(9):1222–1227. doi:10.1016/j.jpsychires.2013.04.010.
Kraft JB, Slager SL, McGrath PJ, Hamilton SP. 2005. Sequence analysis of the serotonin transporter and associations with antidepressant response. Biol Psychiatry. 58(5):374–381. doi:10.1016/j.biopsych.2005.04.048.
Kundakovic M, Rocks D. 2022. Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms. Front Neuroendocrinol. 66:101010. doi:10.1016/j.yfrne.2022.101010.
Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. 2002. Effect of sunlight and season on serotonin turnover in the

brain. Lancet. 360(9348):1840–1842. doi:10.1016/s0140-6736(02)11737-5.

Lee DY, Teyssier C, Strahl BD, Stallcup MR. 2005. Role of protein methylation in regulation of transcription. Endocr Rev. 26(2):147–170. doi:10.1210/er.2004-0008.

Lim ASP. 2021. Diurnal and seasonal molecular rhythms in the human brain and their relation to alzheimer disease. Handb Clin Neurol. 179:271–284. doi:10.1016/B978-0-12-819975-6.00017-0.

Matheson GJ, Schain M, Almeida R, Lundberg J, Cselényi Z, Borg J, Varrone A, Farde L, Cervenka S. 2015. Diurnal and seasonal variation of the brain serotonin system in healthy male subjects. Neuroimage. 112:225–231. doi:10.1016/j.neuroimage.2015.03.007.

Mc Mahon B, Andersen SB, Madsen MK, Hjordt LV, Hageman I, Dam H, Svarer C, da Cunha-Bang S, Baare W, Madsen J, et al. 2016. Seasonal difference in brain serotonin transporter binding predicts symptom severity in patients with seasonal affective disorder. Brain. 139(Pt 5):1605–1614. doi:10.1093/brain/aww043.

Mc Mahon B, Nørgaard M, Svarer C, Andersen SB, Madsen MK, Baaré WFC, Madsen J, Frokjaer VG, Knudsen GM. 2018. Seasonality-resilient individuals downregulate their cerebral 5-HT transporter binding in winter – a longitudinal combined 11C-DASB and 11C-SB207145 PET study. Eur Neuropsychopharmacol. 28(10):1151–1160. doi:10.1016/j.euroneuro.2018.06.004.

Mersch PP, Middendorp HM, Bouhuys AL, Beersma DG, van den Hoofdakker RH. 1999. Seasonal affective disorder and latitude: a review of the literature. J Affect Disord. 53(1):35–48. doi:10.1016/s0165-0327(98)00097-4.

Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, Beekman ATF, Smit JH, Penninx BWJH. 2014. The association between low vitamin D and depressive disorders. Mol Psychiatry. 19(4):444–451. doi:10.1038/mp.2013.36.

Morin LP. 1999. Serotonin and the regulation of mammalian circadian rhythmicity. Ann Med. 31(1):12–33. doi:10.3109/07853899909019259.

Nair-Shalliker V, Dhillon V, Clements M, Armstrong BK, Fenech M. 2014. The association between personal sun exposure, serum vitamin D and global methylation in human lymphocytes in a population of healthy adults in South Australia. Mutat Res. 765:6–10. doi:10.1016/j.mrfmmm.2014.04.001.

Okada S, Morinobu S, Fuchikami M, Segawa M, Yokomaku K, Kataoka T, Okamoto Y, Yamawaki S, Inoue T, Kusumi I, et al. 2014. The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. J Psychiatr Res. 53:47–53. doi:10.1016/j.jpsychires.2014.02.002.

Ouellet-Morin I, Wong CCY, Danese A, Pariante CM, Papadopoulos AS, Mill J, Arseneault L. 2013. Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins. Psychol Med. 43(9):1813–1823. doi:10.1017/S0033291712002784.

Praschak-Rieder N, Willeit M, Wilson AA, Houle S, Meyer JH. 2008. Seasonal variation in human brain serotonin transporter binding. Arch Gen Psychiatry. 65(9):1072–1078. doi:10.1001/archpsyc.65.9.1072.

Provenzi L, Giorda R, Beri S, Montirosso R. 2016. SLC6A4 methylation as an epigenetic marker of life adversity exposures in humans: a systematic review of literature. Neurosci Biobehav Rev. 71:7–20. doi:10.1016/j.neubiorev.2016.08.021.

Raheja SK, King EA, Thompson C. 1996. The Seasonal Pattern Assessment Questionnaire for identifying seasonal affective disorders. J Affect Disord. 41(3):193–199.

Ricceri F, Trevisan M, Fiano V, Grasso C, Fasanelli F, Scoccianti C, De Marco L, Tos AG, Vineis P, Sacerdote C. 2014. Seasonality modifies methylation profiles in healthy people. PLoS One. 9(9):e106846. doi:10.1371/journal.pone.0106846.

Rosenthal NE, Mazzanti CM, Barnett RL, Hardin TA, Turner EH, Lam GK, Ozaki N, Goldman D. 1998. Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. Mol Psychiatry. 3(2):175–177. doi:10.1038/sj.mp.4000360.

Ruhé HG, Booij J, Reitsma JB, Schene AH. 2009. Serotonin transporter binding with [123I]beta-CIT SPECT in major depressive disorder versus controls: effect of season and gender. Eur J Nucl Med Mol Imaging. 36(5):841–849. doi:10.1007/s00259-008-1057-x.

Schiele MA, Kollert L, Lesch KP, Arolt V, Zwanzger P, Deckert J, Ziegler C, Domschke K. 2019. Hypermethylation of the serotonin transporter gene promoter in panic disorder-Epigenetic imprint of comorbid depression? Eur Neuropsychopharmacol. 29(10):1161–1167. doi:10.1016/j.euroneuro.2019.07.131.

Schiele MA, Zwanzger P, Schwarte K, Arolt V, Baune BT, Domschke K. 2021. Serotonin transporter gene promoter hypomethylation as a predictor of antidepressant treatment response in major depression: a replication study. Int J Neuropsychopharmacol. 24(3):191–199. doi:10.1093/ijnp/pyaa081.

Schneider I, Kugel H, Redlich R, Grotegerd D, Bürger C, Bürkner P-C, Opel N, Dohm K, Zaremba D, Meinert S, et al. 2018. Association of serotonin transporter gene AluJb methylation with major depression, amygdala responsiveness, 5-HTTLPR/rs25531 polymorphism, and stress. Neuropsychopharmacology. 43(6):1308–1316. doi:10.1038/npp.2017.273.

Schraut KG, Jakob SB, Weidner MT, Schmitt AG, Scholz CJ, Strekalova T, El Hajj N, Eijssen LM, Domschke K, Reif A, et al. 2014. Prenatal stress-induced programming of genome-wide promoter DNA methylation in 5-HTT-deficient mice. Transl Psychiatry. 4(10):e473. doi:10.1038/tp.2014.107.

Spies M, James GM, Vraka C, Philippe C, Hienert M, Gryglewski G, Komorowski A, Kautzky A, Silberbauer L, Pichler V, et al. 2018. Brain monoamine oxidase A in seasonal affective disorder and treatment with bright light therapy. Transl Psychiatry. 8(1):198. doi:10.1038/s41398-018-0227-2.

Spies M, Knudsen GM, Lanzenberger R, Kasper S. 2015. The serotonin transporter in psychiatric disorders: insights from PET imaging. Lancet Psychiatry. 2(8):743–755. doi:10.1016/S2215-0366(15)00232-1.

Spindelegger C, Stein P, Wadsak W, Fink M, Mitterhauser M, Moser U, Savli M, Mien LK, Akimova E, Hahn A, et al. 2012. Light-dependent alteration of serotonin-1A receptor binding in cortical and subcortical limbic regions in the human brain. World J Biol Psychiatry. 13(6):413–422. doi:10.3109/15622975.2011.630405.

Thorn L, Evans P, Cannon A, Hucklebridge F, Clow A. 2011. Seasonal differences in the diurnal pattern of cortisol secretion in healthy participants and those with self-assessed seasonal affective disorder. Psychoneuroendocrinology. 36(6):816–823. doi:10.1016/j.psyneuen.2010.11.003.

Tyrer AE, Levitan RD, Houle S, Wilson AA, Nobrega JN, Rusjan PM, Meyer JH. 2016. Serotonin transporter binding is reduced in seasonal affective disorder following light therapy. Acta Psychiatr Scand. 134(5):410–419. doi:10.1111/acps.12632.

Vandiver AR, Irizarry RA, Hansen KD, Garza LA, Runarsson A, Li X, Chien AL, Wang TS, Leung SG, Kang S, et al. 2015. Age and sun exposure-related widespread genomic blocks of hypomethylation in nonmalignant skin. Genome Biol. 16(1):80. doi:10.1186/s13059-015-0644-y.

Wankerl M, Miller R, Kirschbaum C, Hennig J, Stalder T, Alexander N. 2014. Effects of genetic and early environmental risk factors for depression on serotonin transporter expression and methylation profiles. Transl Psychiatry. 4(6):e402. doi:10.1038/tp.2014.37.

Willeit M, Sitte HH, Thierry N, Michalek K, Praschak-Rieder N, Zill P, Winkler D, Brannath W, Fischer MB, Bondy B, et al. 2008. Enhanced serotonin transporter function during depression in seasonal affective disorder. Neuropsychopharmacology. 33(7): 1503–1513. doi:10.1038/sj.npp.1301560.

Won E, Choi S, Kang J, Kim A, Han KM, Chang HS, Tae WS, Son KR, Joe SH, Lee MS, et al. 2016. Association between reduced white matter integrity in the corpus callosum and serotonin transporter gene DNA methylation in medication-naive patients with major depressive disorder. Transl Psychiatry. 6(8):e866. doi:10.1038/tp.2016.137.

Xu R, Li S, Li S, Wong EM, Southey MC, Hopper JL, Abramson MJ, Guo Y. 2021. Ambient temperature and genome-wide DNA methylation: a twin and family study in Australia. Environ Pollut. 285:117700. doi:10.1016/j.envpol.2021.117700.

Zhao J, Goldberg J, Bremner JD, Vaccarino V. 2013. Association between promoter methylation of serotonin transporter gene and depressive symptoms: a monozygotic twin study. Psychosom Med. 75(6):523–529. doi:10.1097/PSY.0b013e3182924cf4.

Ziegler C, Richter J, Mahr M, Gajewska A, Schiele MA, Gehrmann A, Schmidt B, Lesch KP, Lang T, Helbig-Lang S, et al. 2016. MAOA gene hypomethylation in panic disorder-reversibility of an epigenetic risk pattern by psychotherapy. Transl Psychiatry. 6(4):e773. doi:10.1038/tp.2016.41.