ORIGINAL ARTICLE

Seasonal Variation in Human Brain Serotonin Transporter Binding

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Context: It is a common experience in temperate zones that individuals feel happier and more energetic on bright and sunny days and many experience a decline in mood and energy during the dark winter season. Brain serotonin is involved in the regulation of physiologic functions, such as mating, feeding, energy balance, and sleep. Although these behaviors and serotonin-related conditions show a clear seasonal pattern in humans, the molecular background of seasonal changes in serotonin function is entirely unknown. The serotonin transporter is a key element in regulating intensity and spread of the serotonin signal.

Objectives: To detect seasonal variations in serotonin transporter binding in the living human brain and to detect correlations between serotonin transporter binding and duration of daily sunshine.

Design: Regional serotonin transporter binding potential values, an index of serotonin transporter density, were assessed from December 1, 1999, to December 9, 2003, in a consecutive sample of healthy volunteers. Binding potential values were related to meteorologic data.

Setting: Tertiary care psychiatric hospital.

Participants: Volunteer sample of 88 drug-naïve healthy individuals.

Intervention: Carbon 11–labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile positron emission tomography.

Main Outcome Measure: Regional serotonin transporter binding potential values.

Results: Serotonin transporter binding potential values were significantly higher in all investigated brain regions in individuals investigated in the fall and winter compared with those investigated in the spring and summer ($P = .01$ to $.001$). Moreover, binding potential values showed negative correlations with average duration of daily sunshine in all brain regions ($\rho = -0.21$ to -0.39; $P = .05$ to $< .001$), such that higher values occurred at times of lesser light.

Conclusions: Serotonin transporter binding potential values vary throughout the year with the seasons. Since higher serotonin transporter density is associated with lower synaptic serotonin levels, regulation of serotonin transporter density by season is a previously undescribed physiologic mechanism that has the potential to explain seasonal changes in normal and pathologic behaviors.

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INDOLAMINES (TRYPTOPHAN, SEROtonin, melatonin, and related compounds) have transduced light signals and information on photoperiod into organisms and cells since early in evolution,[1] and their role in signaling change of seasons is preserved in humans.[2] Serotonin is involved in the regulation of many physiologic and pathologic behaviors that vary with season in clinical and nonclinical populations.[3-12] Seasonal variations in peripheral serotonergic markers have been demonstrated in several studies.[12-14] A postmortem study[15] shows seasonal differences in serotonin concentration in the human hypothalamus; another study[16] suggests that sunlight alters serotonin turnover in the human brain.

The serotonin transporter clears the synaptic cleft from serotonin and, therefore, has an important role in the regulation of serotonergic neurotransmission.[17] Given the role of the serotonin transporter, the seasonal variation in serotonin-related behaviors,[3-12] and the seasonal variation in brain serotonin concentrations and other serotonin markers,[12-16] we hypothesized that there is a seasonal variation in regional serotonin transporter binding potential values in the living human brain. As a secondary hypothesis, we expected to find a correlation between serotonin transporter binding po-

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tential values and the duration of sunshine throughout the year. The serotonin transporter binding potential (which is also referred to as 5-HTT BP_{ND}[18]) is an index of serotonin transporter levels and is defined as $f_{ND} \times B_{avail}/K_d$, where f_{ND} is the free fraction of radioligand in the nondisplaceable compartment; B_{avail}, the concentration of available transporter; and K_d, the dissociation constant.

Previous investigations[19,20] of regional serotonin transporter binding and season in humans have not led to a clear understanding of the relationship between these 2 measures. The techniques applied were not optimally sensitive, and the results were in opposite directions. A study[21] using the nonspecific monoamine transporter ligand iodine 123–labeled 2-β-carboxymethoxy-3-β-(4-iodophenyl)-tropane and single-photon emission computed tomography reported increased serotonin transporter binding during summer in healthy women. A subsequent carbon 11–labeled McN5652 ([^{11}C]McN5652) positron emission tomography (PET) study[22] reported no seasonal change in serotonin transporter binding in the thalamus and, in a subset of analyses, a seasonal change in serotonin transporter binding in the mesencephalon such that serotonin transporter binding was lower in spring and summer. The authors of the second study[22] reported that no other brain regions were assessable. Limitations of [^{11}C]McN5652 PET include a modest ratio of specific binding relative to free and nonspecific binding and slow pharmacokinetics,[23] which may reduce the ability of this method to detect significant effects.[19]

The highly selective PET serotonin transporter ligand carbon 11–labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C]DASB[24]) allows valid and reliable in vivo measurement of serotonin transporter binding potential values in cortical and subcortical brain regions[25-27] and is the optimal method for quantification of serotonin transporter binding potential values in humans.[20,25,28] To definitively address the question of whether brain serotonin transporter binding relates to season, we conducted a retrospective study in a large sample of healthy control subjects (N=88) living in the greater Toronto area, measuring serotonin transporter binding in multiple regions of interest (ROIs), many of which have dense serotonergic innervation (anteromedial prefrontal cortex, anterior cingulate cortex, caudate, putamen, thalamus, and mesencephalon).

METHODS

STUDY PARTICIPANTS AND EXPERIMENTS

All study participants (41 women and 47 men; mean [SD] age, 33.0 [8.9] years; age range, 20-51 years) gave informed consent according to procedures approved by the ethics board of the University of Toronto. Between December 1, 1999, and December 9, 2003, they were enrolled in various studies as healthy controls, were physically healthy, had no history of alcohol or other substance abuse, and were lifetime naïve for antidepressant and antipsychotic agents. Participants underwent screening (Structured Clinical Interview for *DSM-IV*-Non-Patient Edition)[29] to rule out psychiatric disorders (current or in remission), current suicidal ideation, and history of self-harm behavior, anger dyscontrol, or impulsive behavior. All 88 study participants underwent a single [^{11}C]DASB PET scan in a medication-free state. The same protocols for participant preparation, PET acquisition, image reconstruction, and tracer kinetic modeling were applied for each participant.

Synthesis of [^{11}C]DASB measurement of serotonin transporter binding potential with [^{11}C]DASB PET scanner and methods reported in this study are the same as those used in previous studies.[26,30-35] The ROIs were delineated using an automated software program,[32] as described previously. The posterior half of the cerebellar cortex under exclusion of vermis and cerebellar white matter served as the reference region. We also kept at least 1 full width at half maximum (5.5 mm) from the venous sinuses and occipital cortex. At a distance of 1 full width at half maximum, spillover from the occipital cortex (which has specific binding) or the venous sinuses is negligible.

Serotonin transporter binding potential values were determined using the Logan noninvasive method[36] implemented within computer software (PMOD; PMOD Technologies Ltd, Zurich, Switzerland). This analysis method provides valid and reproducible [^{11}C]DASB PET measurements of serotonin transporter binding potential values with low between-subject variance in serotonin transporter binding potential for most brain regions.[32-35] An additional analysis was performed using the modified simplified reference tissue method (SRTM-2[27,37]) in a data subset. Analysis of intraclass correlation coefficients showed good agreement for the 2 analysis methods (prefrontal cortex, 0.98; cingulate cortex, 0.98; caudate, 0.87; putamen, 0.91; and thalamus, 0.94). Between-subject variability of mesencephalon serotonin transporter binding potential determined with the SRTM-2 model was overly elevated in this data set, so only the Logan method was applied to determine serotonin transporter binding potential in the mesencephalon.

STATISTICAL ANALYSIS

Individual scans were grouped according to season of scan with the equinoxes as the cutoff between the fall and winter season and the spring and summer season: for fall and winter, the scan dates were September 23 to March 20 (n=38), and for spring and summer, the scan dates were March 21 to September 22 (n=50). In the initial step, age, sex, and season of scan (fall and winter vs spring and summer) were entered into a logistic regression model separately for all 6 ROIs because some studies[32,38] have suggested an influence of age and sex on brain serotonin transporter binding. Because sex had no effect in the regression model in any of the ROIs even at most liberal probability thresholds, a final analysis of covariance was performed using season of scan as the between-subjects variable and age as the covariate. For clarity, results of a separate analysis of variance for season of scan, age, and sex are given in **Table 1**. Two-tailed *t* tests were used for post hoc comparisons of serotonin transporter binding potential values in the fall and winter and spring and summer groups after testing for normal distribution of data (the Levene test was not statistically significant for all 6 ROIs; $F_{1,86}$=0.001 to 0.49; P=.97 to .49).

Meteorologic data on duration of sunshine, length of day, temperature, and humidity were obtained from the Ontario Climate Centre, Toronto. Detailed records of total sunlight radiation in the Toronto area for each day were available for a limited period only. Thus, data of mean monthly sunshine duration in a period of 30 years (1971-2000; Environment Canada; http://www.climate.weatheroffice.ec.gc.ca/climate_normals/results_e.html; 2004) were interpolated to obtain a value for each day of the year. Spearman rank sum correlations were then calculated for duration of average daily sunshine, the other climatic variables, and serotonin transporter binding potential values in each ROI.

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Table 1. Effects of Season (Spring and Summer vs Fall and Winter) and Age on Brain Serotonin Transporter Binding Potentials Measured With [^{11}C]DASB and Positron Emission Tomography in 88 Healthy Study Participants

Brain Region	Season		Age		Sex		Overall Model Season and Age	
	$F_{1,86}$	*P* Value	$F_{1,86}$	*P* Value	$F_{1,86}$	*P* Value	$F_{2,85}$	*P* Value
Anteromedial prefrontal cortex	6.88	.01	3.42	.07	0.001	.97	5.25	.007
Anterior cingulate cortex	6.46	.01	3.88	.05	0.02	.89	5.23	.007
Caudate	13.01	.001	3.83	.05	1.40	.24	8.76	<.001
Putamen	9.67	.003	5.77	.02	0.04	.84	8.13	<.001
Thalamus	7.40	.008	5.00	.03	0.13	.72	6.43	.003
Mesencephalon	10.17	.002	7.05	.009	0.03	.86	9.19	<.001

Abbreviation: [^{11}C]DASB, carbon 11–labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile.

Table 2. Group Differences in Brain Serotonin Transporter Binding Potentials in Healthy Study Participants Undergoing Positron Emission Tomography in Spring and Summer or Fall and Winter

Brain Region	Binding Potential, Mean (SD)		*P* Value[a]	Relative Difference (Spring and Summer vs Fall and Winter), %	Peak Month Difference,[b] %
	Spring and Summer	Fall and Winter			
Anteromedial prefrontal cortex	0.20 (0.05)	0.22 (0.05)	.02	12.2	38.5
Anterior cingulate cortex	0.24 (0.07)	0.27 (0.06)	.03	13.1	38.7
Caudate	0.93 (0.17)	1.06 (0.17)	<.001	14.3	35.0
Putamen	0.93 (0.15)	1.03 (0.18)	.004	10.8	22.1
Thalamus	1.04 (0.19)	1.14 (0.19)	.007	10.6	39.6
Mesencephalon	1.46 (0.34)	1.69 (0.35)	.002	16.1	41.5

[a] Two-tailed *t* test.
[b] Calculated as follows: (binding potential at peak month – binding potential at trough month)/binding potential at trough month × 100.

RESULTS

We found that serotonin transporter binding potential values were higher in all analyzed ROIs in individuals who underwent scanning during fall and winter when compared with those who underwent scanning in spring and summer. The effects of season (fall and winter vs spring and summer) on serotonin transporter binding potential values in an analysis of variance gave strongly significant results in all investigated ROIs ($F_{1,86}$=6.46 to 13.01; P=.01 to <.001) (Table 1). An overall analysis of covariance (ANCOVA) on the effects of age and season (fall and winter vs spring and summer) on serotonin transporter binding potential values gave significant results in all investigated ROIs ($F_{2,85}$=5.23 to 9.19; P=.007 to <.001) (Table 1). As expected, a modest decrease of serotonin transporter binding potential values occurred with age in all ROIs (Pearson product moment correlation coefficient r=–0.20 to –0.28; P=.05 to .009). In the ANCOVA, age significantly affected serotonin transporter binding potential values in the putamen, thalamus, and mesencephalon; the effect was found at a trend level in other ROIs (Table 1). Sex did not relate to serotonin transporter binding potential values (Table 1). Post hoc comparisons showed consistently higher serotonin transporter binding potential values in all ROIs (from 10.6% to 16.1%) in study participants who underwent scanning in the fall and winter; the largest relative difference was found in the mesencephalon (**Table 2**).

Although the lowest serotonin transporter binding potential values were consistently measured in June, peak months were more variable across ROIs. Serotonin transporter binding potential values peaked in the putamen in November, in the mesencephalon in December, in the caudate in January, and in the prefrontal cortex, thalamus, and cingulate cortex in February or March. Serotonin transporter binding potential values decreased uniformly throughout the investigated brain regions between March and June. Graph analysis showed reciprocal coincidence of peaks and troughs for the average duration of daily sunshine and regional serotonin transporter binding potential values (**Figure**). Serotonin transporter binding potential values showed significant negative correlations with average duration of daily sunshine and day length (**Table 3**), indicating reductions in serotonin transporter density with increasing duration of sunshine. To some extent, serotonin transporter binding potential values correlated positively with humidity on scan days (prefrontal cortex: ρ=0.23, P=.03; cingulate cortex: ρ=0.24, P=.03; caudate: ρ=0.28, P=.009; putamen: ρ=0.26, P=.01; thalamus: ρ=0.07, P=.55; mesencephalon: ρ=0.14, P=.18), whereas no correlations were found with temperature (data not shown). Duration of sunshine and day length were correlated (ρ=0.97; P<.001). Duration of sunshine correlated significantly with humidity (ρ=–0.36 to –0.42; P<.001) and temperature (ρ=0.65 to 0.66; P<.001). No significant correlations were found between humidity and temperature measures.

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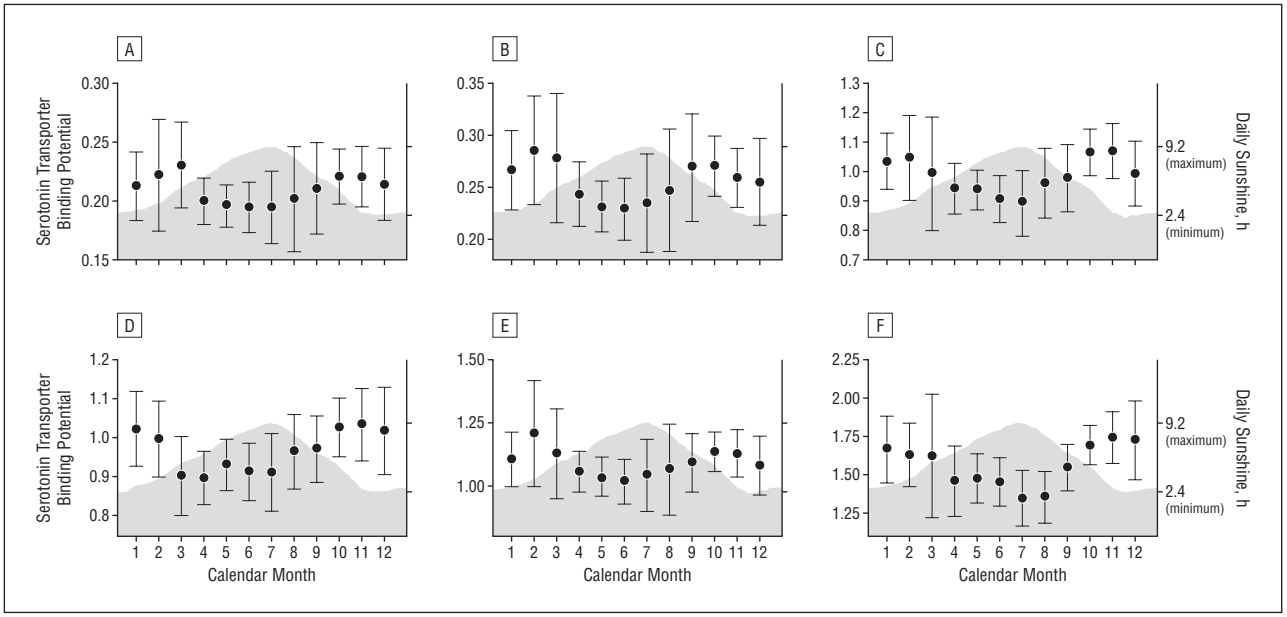

Figure. Reciprocal peaks and troughs of brain serotonin transporter binding and duration of sunshine in the 88 healthy study participants. Serotonin transporter binding potential values were measured using the selective serotonin transporter radioligand carbon 11–labeled 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile and positron emission tomography. The serotonin transporter binding potential values were determined in 6 brain regions (anteromedial prefrontal cortex [A], anterior cingulate cortex [B], caudate [C], putamen [D], thalamus [E], and mesencephalon [F]). Circles represent bimonthly moving average means of serotonin transporter binding potential values; error bars, 95% confidence intervals of the mean. The shaded areas represent the average duration of sunshine in Toronto, Ontario, Canada (range, 2.4-9.2 hours a day). There were 38 study participants in the fall and winter seasons and 50 in the spring and summer seasons. The number of study participants for each bimonthly data point was as follows: January, 11; February, 4; March, 6; April, 14; May, 23; June, 24; July, 14; August, 8; September, 13; October, 28; November, 21; and December, 10.

Table 3. Negative Correlations Between Average Duration of Sunshine and Day Length in Toronto, Ontario, Canada, and Brain Serotonin Transporter Binding Potentials in the 88 Healthy Study Participants

	Duration of Sunshine[a]		Day Length[a]	
Brain Region	ρ[b]	*P* Value	ρ[b]	*P* Value
Anteromedial prefrontal cortex	−0.21	.05	−0.20	.06
Anterior cingulate cortex	−0.21	.05	−0.21	.05
Caudate	−0.26	.01	−0.29	.007
Putamen	−0.23	.03	−0.26	.01
Thalamus	−0.21	.05	−0.21	.06
Mesencephalon	−0.39	<.001	−0.38	<.001

[a] No significant correlation was found between age and duration of sunlight ($r = 0.06$, $P = .60$) or between age and day length ($r = 0.01$, $P = .91$).
[b] Spearman rank sum correlation coefficient.

COMMENT

This study shows that brain serotonin transporter binding is higher in healthy individuals investigated in the fall and winter compared with those investigated in the spring and summer in all brain regions examined. Moreover, we show that regional serotonin transporter binding potential values correlate negatively with average duration of daily sunshine, such that higher serotonin transporter binding potential values occur at times of lesser light. Given that the serotonin transporter has a role in clearing extracellular serotonin, these findings have important implications for understanding seasonal mood change in healthy individuals, vulnerability to seasonal affective disorder, and the relationship of light exposure to mood. These findings also have significant implications for the design of future studies relating serotonin transporter binding to psychiatric illness and genotype.

An implication of greater serotonin transporter binding in winter is that this may facilitate extracellular serotonin loss during winter, leading to lower mood. There is an inverse relationship between available serotonin transporter binding and clearance of extracellular serotonin because serotonin reuptake inhibitor antidepressants increase extracellular serotonin levels,[39] serotonin transporter knockout mice have greater extracellular serotonin levels,[40,41] and mice with overexpression of serotonin transporter have low extracellular serotonin levels.[42] Therefore, higher regional serotonin transporter binding potential values in fall and winter may explain hyposerotonergic symptoms, such as lack of energy, fatigue, overeating, and increased duration of sleep during the dark season. From this perspective, greater serotonin transporter binding potential may be viewed as a contributing factor for lowering extracellular serotonin

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levels, which may be particularly important when other factors, such as greater intracellular degradation of serotonin, happen to be present.[43] This offers a possible explanation for the regular reoccurrence of depressive episodes in fall and winter in some vulnerable individuals.[44]

Consistent, significant correlations were found between regional serotonin transporter binding potential and daily duration of sunlight. Although the nature of our data precludes causal inference, evidence in rodents shows that light can directly modify the processing of serotonergic stimuli[45] and suggests that light is associated with downregulation of brain serotonin transporter density in some brain regions.[46] Independent of the underlying mechanism, a reduction in serotonin transporter numbers is expected to be similar in its consequences to a pharmacologic serotonin transporter blockade, a mechanism of action shared by many antidepressant medications. Many antidepressants reduce serotonin transporter binding because they have a high affinity for the serotonin transporter[47,48] and substantial serotonin transporter occupancy.[31,33]

Endogenous displacement has been observed in a small percentage of radiotracers, and the question could be raised of whether seasonal changes in endogenous serotonin levels may contribute to the seasonal variation in [^{11}C]DASB binding potential. We think that the likelihood of a significant influence of endogenous serotonin on [^{11}C]DASB binding potential values in humans under physiologic conditions is exceedingly unlikely because [^{11}C]DASB binding potential is unaffected by tryptophan depletion in humans.[34,49] Changing extracellular serotonin levels by several hundred percent or more in animal models with paradigms not tolerated by humans has some effect on [^{11}C]DASB binding potential,[20,50-53] but such changes are outside the magnitude of seasonal brain serotonin changes reported by Carlsson et al[15] in humans (Meyer[20] provides a further review).

The interpretations made in this study have some limitations. The serotonin transporter binding potential is an index of both density and affinity, so it is theoretically possible that the seasonal variation in serotonin transporter binding potential is related to either. Even so, both parameters have functional contributions because decreasing affinity or density of serotonin transporter can increase serotonin concentrations near serotonin transporters.[54] This study also focuses considerably on the correlation between daily duration of sunshine and change in serotonin transporter binding potential (in contrast to temperature or humidity), and the correlation may exist because daily duration of sunshine and serotonin transporter binding potential each separately correlate with seasonal change. However, there are additional reasons to focus on daily duration of sunshine: light exposure may influence serotonin transporter binding and serotonin reuptake in some brain regions in rodents, and light exposure has a reciprocal relationship with the processing of serotonergic stimuli.[45,46,55-57]

A spring peak in suicide rate in the northern hemisphere has been described by several independent researchers.[58-62] This peak appears shifted for 6 months in the southern hemisphere (also occurring in spring)[63] and absent in equatorial regions.[64] Given that we report a shift toward decreasing regional serotonin transporter binding potential in springtime, a future study should consider whether such a shift contributes toward increasing suicide risk. It seems paradoxical that a process theorized to increase synaptic serotonin could lead to increased suicidality. However, psychopharmacologic effects of short-term serotonin transporter blockade in animals vary depending on the anatomical location of serotonin transporter blockade in the brain. For example, as a result of serotonin 1A receptor–mediated somatodendritic autoinhibition, short-term serotonin transporter blockade in the brainstem has been shown to reduce serotonin outflow in prefrontal brain areas,[65] which are implicated in control of impulsivity and aggression.[66]

The present study also has important implications for the design of future studies of serotonin transporter binding. For investigations of regional brain serotonin transporter binding comparing healthy individuals with those with psychiatric illness, it would be useful to sample healthy individuals evenly throughout the different seasons to avoid a bias of seasonal effect. For investigations of the relationship between genotype and serotonin transporter binding, introducing either duration of daily sunlight or a light-dark season as a separate predictor variable may help remove variance. Results in a genotyped subsample of white individuals[35] from the present study show promise for this approach: The effects of the L_A/L_A genotype of the serotonin transporter–linked polymorphic region and duration of daily sunlight on regional serotonin transporter binding potential in these 30 individuals in an ANCOVA model were assessed in a reexamination of these data, with daily duration of sunlight as a covariate and presence of the L_A/L_A genotype as a factor. Sunlight exposure had a stronger relationship, but the L_A/L_A genotype also showed significant effects on serotonin transporter binding potential in the putamen (effect of genotype: $F_{1,27}=11.8$, $P=.002$) and trended to significance in the thalamus (effect of genotype: $F_{1,27}=3.2$, $P=.08$) and the caudate (effect of genotype: $F_{1,27}=2.9$, $P=.10$).

In conclusion, according to our data, regional serotonin transporter binding in the human brain is dynamic, being greater during the fall and winter and lower during the spring and summer. Taking this dynamic into account will improve our understanding of the role of the serotonin transporter in the pathogenesis and treatment of psychiatric disorders with seasonal onset. For example, a potential implication of greater serotonin transporter binding potential in the winter is that this may facilitate extracellular serotonin loss during winter, leading to lower mood. Among the environmental variables that change with season, duration of sunlight is suspected of being mechanistically related given the significant correlations between sunlight duration and regional serotonin transporter binding potential and the reciprocal relationship of light with the processing of serotonergic stimuli.[45,46,55-57] Future in vivo and postmortem studies investigating the role of serotonin transporter in psychiatric disorders should consider season as a factor in their design, which would be expected to enhance consistency of results across studies.[20,67] In summary, our data show that in addition to genes[35,68] and their

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interaction with life events,[69-71] season is another important factor that contributes to the serotonergic tone in the living human brain.

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