Neuroimaging in Seasons and Winter Depression

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Abstract

Seasonal fluctuations in mood, behaviour, energy level and appetite are common in humans living in temperate and polar zones. These changes are not necessarily associated with clinical symptoms; however, some people regularly experience severe changes in mood and drive during the dark season. Seasonal affective disorder (SAD) is regarded as an extreme reaction to changes in environmental light. The underlying mechanism of these seasonal changes and the pathobiology of *SAD* still remain unclear. However, several lines of evidence suggest a key role of monoamines in modulating seasonal fluctuations in animals and humans. Here, we review the literature on neuroimaging including MRI, SPECT and PET in SAD. Furthermore, the effects of season on the monoamine neurotransmitter systems serotonin and dopamine are discussed.

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8.1 Introduction

Seasonal fluctuations in metabolism and behaviour are common in organisms living in temperate and polar zones. These fluctuations are evolutionary coping strategies, necessary for adapting to dramatic changes in temperature, light and food availability (Levitan et al. 2006, 2010; Praschak-Rieder and Willeit 2012). The degree of this adaptation in humans is known as "seasonality". Seasonal changes in mood, behaviour, energy level and appetite are not necessarily associated with psychopathological symptoms, as they are normally distributed in the general population (Hardin et al. 1991; Kasper et al. 1989; Praschak-Rieder and Willeit 2012; Winkler et al. 2002). Extreme seasonal variations in mood and drive were first described in a psychiatric context by Rosenthal et al. (1984). "Seasonal affective disorder" (SAD) is considered a clinical subtype of major depression. A milder form of SAD, termed "winter blues" or "subsyndromal SAD (s-SAD)", was described by Kasper and colleagues (1988). Altogether, prevalence rates of SAD and s-SAD have been reported between 1.5 and 17.8 % in the Northern Hemisphere (Kasper 1994). Based on the hypothesis that SAD is triggered by photoperiod variations and the fact that these variations are larger in higher latitudes closer to the poles, increased prevalence rates of SAD have been assumed in these regions (Mersch et al. 1999). Although, some studies found a significant positive correlation between latitude and prevalence of SAD (Potkin et al. 1986; Rosen et al. 1990), climate, social as well as cultural factors seem to have a more considerable impact on its prevalence (Mersch et al. 1999). Gender disparity is substantially greater in SAD than in other forms of depression with a female-to-male sex ratio of up to 9:1 according to some studies (Boyce and Parker 1988; Thompson and Isaacs 1988; Winkler et al. 2002; Wirz-Justice et al. 1986).

The "winter seasonal pattern" constitutes the most common form of SAD. According to DSM-IV, this form of SAD is characterised by a recurrent pattern of major depressive episodes during fall and winter (in the absence of seasonal psychosocial stressors) and remission of depressive symptoms during spring and summer (Rosenthal et al. 1984; Lam and Levitan 2000). In contrast to the winter form of SAD, Wehr described a less prevalent form of SAD with depressive symptoms during summer and hypomania during winter (Wehr et al. 1987). Furthermore, seasonal depressive symptoms are reported with a higher frequency during summer and attributed to intense heat and humidity in some parts of the world (Avasthi et al. 2001; Morrissey et al. 1996). On a symptom level, winter SAD is frequently characterised by atypical depressive symptoms such as increased sleep duration, hyperphagia and subsequent weight gain (Praschak-Rieder and Willeit 2003; Rosenthal et al. 1984). In parallel to non-seasonal depression, the neurotransmitters serotonin, norepinephrine and dopamine have been suggested to play a crucial role in the aetiology and pathophysiology of SAD (Levitan 2007). A transient decline in brain serotonin due to depletion of tryptophan, the amino acid precursor of serotonin, has been reported to result in lower mood and increased irritability or aggressive responding in several studies (for review, see Young and Leyton 2002). Tryptophan

depletion caused a relapse of depressive symptoms in remitted SAD patients (Neumeister et al. 1998a) and reversed the therapeutic effect of bright light treatment (Lam et al. 1996; Neumeister et al. 1998b). Alterations in norepinephrine and dopamine neurotransmission were hypothesised to be essential for the occurrence of fatigue and reduced levels of subjective arousal in SAD patients (for review, see Levitan 2007). In addition, dopamine has been reported to act as a chemical messenger for light adaptation (Witkovsky 2004). Patients with SAD show reduced light sensitivity (Hebert et al. 2004), supporting the hypothesis of an involvement of dopamine in the pathogenesis of SAD.

Based on evidence derived from several randomised, placebo-controlled studies using dim light or deactivated ion generators as comparator, light therapy is recognised as an effective therapy and is recommended as first-line treatment for SAD (Lewy et al. 1998; Terman 2006; Terman et al. 1989). The pathophysiology of SAD is still not sufficiently understood (Magnusson and Partonen 2005), though theories on its pathogenesis are intimately tied to the biological mechanisms of light therapy (Lam and Levitan 2000).

Although SAD and its subsyndromal form show a high prevalence, imaging studies investigating patients with SAD and the effects of seasonality on the brain are scarce. The following synopsis will give an overview about neuroimaging in SAD and seasonal effects on brain monoamine pathways.

8.2 Structural and Functional Magnetic Resonance Imaging

8.2.1 Structural MRI Studies

Volumetric studies in non-seasonal depressed patients showed a nonspecific brain atrophy including an increase in ventricular-brain ratio, increased cerebrospinal fluid volume and sulcal atrophy (Steffens and Krishnan 1998). Additionally, a lateralisation of atrophy was found to the left medial temporal lobe in patients with a late-onset depression (Greenwald et al. 1997), whereas other studies were not able to demonstrate grey matter differences in this region (Coffey et al. 1993; Pantel et al. 1997). In addition to the findings of Greenwald, Drevets et al. (1997) were able to show a left-lateralised reduction in grey matter volume in the subgenual prefrontal cortex (Brodmann area 24) in patients with familial forms of major depressive disorder (MDD) and bipolar disorder (BD). The subgenual prefrontal cortex is a region mediating emotional and autonomic responses to socially significant or provocative stimuli. Given the suggested critical role of the hippocampus in the pathophysiology of depression (Campbell and Macqueen 2004), several studies revealed smaller sizes of this region in patients with a depressive episode (Caetano et al. 2004; Frodl et al. 2002b; Shah et al. 1998; Sheline 1996). In addition, contradictory results of structural abnormalities in the amygdala in depression have been shown. An enlargement of the amygdala was found in patients with a first episode of major depression (Frodl et al. 2002a), whereas this enlargement was not found

in recurrent depression (Frodl et al. 2003). A smaller amygdala volume in depressed patients was reported by Sheline et al. (1998). The structural changes in grey matter mentioned above were only found in patients suffering from non-seasonal depression, and there is still a lack of volumetric MRI investigations in the field of SAD.

Only two MRI studies focusing on structural abnormalities in SAD patients were available in the literature. In line with a hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis in depression, larger pituitary volumes have been found in patients with major depression (Krishnan et al. 1991). In contrast to these findings, a study in 19 patients with SAD did not show any significant pituitary volume changes (Schwartz et al. 1997). Since the participants of this study underwent MRI scans of the pituitary gland both in summer and winter, this study was further able to demonstrate that pituitary volumes did not change between seasons, supporting the notion that the aetiology of SAD is associated with factors other than HPA dysregulation (Sheline et al. 1998). Recently, the findings of Schwartz et al. have been replicated in a Brazilian investigation (Miranda-Scippa et al. 2008). Miranda-Scippa and her colleagues compared pituitary gland volumes of 12 patients suffering from SAD and 12 healthy controls matched for age, gender and menstrual cycle. No significant differences in pituitary gland volume between patients and controls were found. Light therapy was shown to significantly reduce depressive symptoms, but it did not alter pituitary gland volumes. Although no significant changes of pituitary volumes have been found in this study, pituitary volumes in winter correlated positively with the severity of depression in patients. While some studies have suggested adrenal gland enlargement in non-seasonal depression (Kessing et al. 2011), to our knowledge, there are no investigations focusing on adrenal gland volumes in SAD.

In sum, recent data on structural changes in SAD provide no clear evidence of structural brain alteration in SAD.

8.2.2 Functional MRI (fMRI) Studies

Electroretinographical studies have shown a reduced retinal light sensitivity in SAD patients (Hebert et al. 2004) with seasonal variations in rod and cone function. Furthermore, a normalisation of rod and cone function was found after 4 weeks of bright light therapy (Lavoie et al. 2009). Based on these findings, Vandewalle et al. (2011) conducted an fMRI study investigating the impact of light on emotional processing in untreated SAD patients ($n = 14$). Patients showed an increased response to auditory emotional stimuli in the posterior hypothalamus under blue light (480 nm) exposure, whereas green light (550 nm) decreased hypothalamic response. Furthermore, increased responsiveness to vocal stimuli was found in thalamus and brainstem areas in patients. The authors suggested that altered emotional processing during coloured light exposure, as shown by the abnormal light responsiveness of the hypothalamus, may constitute a neurobiological substrate of SAD.

8.3 Single Photon Emission Computed Tomography (SPECT)

The monoamine neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in various physiological functions, including regulation of circadian rhythms as well as in the pathophysiology of numerous neuropsychiatric disorders. Based on several findings of a seasonal rhythm in brain and peripheral serotonin (5-HT) activity in humans, this monoamine neurotransmitter was suggested to play a major role in the pathomechanisms of SAD (Kasper et al. 1996; Lam and Levitan 2000; Willeit et al. 2000, 2008). In a human post-mortem study, Carlsson and colleagues were able to show a seasonal variation in hypothalamic 5-HT concentrations with lowest levels of 5-HT occurring in winter (Carlsson et al. 1980). Confirming these findings in vivo, an Australian study by Lambert et al. reported reduced serotonin turnover in the Australian winter months between June and August (Lambert et al. 2002).

One of the key molecules in serotonergic neurotransmission is the serotonin transporter (SERT or 5-HTT). After release of 5-HT into the synaptic cleft, SERT mediates reuptake into the presynaptic neuron. Thereby, SERT activity is able to control spatial and temporal spread of the serotonergic signal. Selective serotonin reuptake inhibitors (SSRIs) exert their antidepressive effect by blocking SERT and show comparable efficacy to light therapy in the treatment of SAD (Lam et al. 2006; Praschak-Rieder and Willeit 2003).

The availability of brain SERT binding sites can be assessed in vivo via the non-specific monoamine transporter ligand [^{123}I]-2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane ([^{123}I]ß-CIT) and single photon emission computed tomography (SPECT; Brucke et al. 1993). By means of this technique, Neumeister et al. first demonstrated seasonal effects on brain SERT binding by investigating a small sample of healthy females ($n = 11$; Neumeister et al. 2000). Variations in the availability of thalamus/hypothalamus SERT binding sites were found between summer and winter with higher SERT availability in summer. A recent study of SERT availability in a larger sample of non-seasonal depressed patients ($n = 49$) demonstrated opposite findings with significantly higher [^{123}I]ß-CIT binding in winter (Ruhe et al. 2009). However, a significant reduction in SERT availability was only shown in male depressed patients.

Only a limited number of SPECT studies have been conducted in patients with SAD. In a study by Willeit et al. (2000), drug-free SAD patients ($n = 11$) showed decreased [^{123}I]ß-CIT binding in the midbrain thalamus-hypothalamus area compared to controls matched for age, gender, menstrual cycle and time of scanning. Based on animal (Laruelle et al. 1993) and post-mortem displacement studies (Staley et al. 1994), [^{123}I]ß-CIT is known to bind predominantly to SERT in the midbrain. Therefore, the finding of Willeit et al. may reflect a reduced SERT availability in untreated depressed patients with SAD in winter, a result that is partly in line with findings in non-seasonal depression (Ruhe et al. 2009). A study on SERT binding in platelets of patients with SAD and healthy controls failed to show differences between the two groups (Willeit et al. 2008). However, this study showed increased efficiency in SERT-mediated 5-HT uptake during winter depression. After

successful light therapy and during natural remission in summer, SERT function returned to control levels.

The dopaminergic system was also suggested to be involved in the pathophysiology of SAD by a [^{123}I]ß-CIT study of the Vienna group (Neumeister et al. 2001). In contrast to the midbrain, [^{123}I]ß-CIT binds—after achieving equilibrium binding (later than in the midbrain)—predominantly to dopamine transporters (DAT) in the striatum. According to that, Neumeister et al. were able to show a reduced availability of striatal DAT in untreated SAD patients in winter time.

A recent SPECT study from Taiwan investigated striatal dopamine $D_{2/3}$ availability in 68 healthy subjects with respect to their exposure to sunshine 30 days prior to their individual SPECT scan (Tsai et al. 2011). Since there is little seasonal variation in day length and daily sunlight in Taiwan, only 35 subjects in the lowest ($n=18$) and highest ($n=17$) quartile of average sunshine duration were analysed. Higher [^{123}I]iodobenzamide ([^{123}I]IBZM) binding was revealed in subjects exposed to higher amounts of sunshine than in those with lower sunshine exposure prior to SPECT scans. Results have to be interpreted with caution: [^{123}I]IBZM is sensitive towards changes in extracellular dopamine levels (Laruelle 2000), and the findings of higher [^{123}I]IBZM binding could either be due to a higher amount of dopamine $D_{2/3}$ receptors or reduced levels in extracellular dopamine. Moreover, rates of tobacco use differed significantly between groups.

Apart from transporter and receptor studies, an investigation on regional cerebral blood flow (rCBF) in a small sample of untreated patients with SAD and healthy controls using [^{99m}Tc]hexamethylpropyleneamine oxime ([^{99m}Tc]HMPAO), and SPECT suggested an increased left frontal rCBF in patients with SAD (Praschak-Rieder et al. 1998). Following successful bright light treatment, normalisation in left frontal rCBF was found.

The mentioned SPECT studies revealed reduced availabilities of SERT and DAT as well as alterations in regional cerebral blood flow in depressed patients with SAD. Moreover, possible seasonal effects on $D_{2/3}$ receptors have been demonstrated in healthy subjects. Findings of these preliminary studies were partly strengthened by results obtained in studies using more selective radioligands and positron emission tomography (PET—see Sect. 8.4). However, independent replications in larger samples of patients with SAD are still warranted.

8.4 Positron Emission Tomography (PET)

During the last decades, only two PET studies specifically investigating patients with SAD were conducted. Both studies on cerebral metabolism used [^{11}F]deoxyglucose ([^{11}F]FDG) to investigate if patients with SAD showed abnormalities in cerebral metabolic rates. A study by Cohen et al. (1992) compared brain metabolic rates between a small sample ($n=7$) of patients with winter SAD and healthy controls. All patients were drug-free for at least 3 months and were investigated in an untreated condition (*off-lights*). Furthermore, six patients were also PET-scanned after at least 10 days of light treatment (*on-lights*). To avoid possible order effects, three patients were investigated in the *off-lights* condition first and after 10 days of

Table 8.1 Neuroimaging in patients with SAD

Method	Author	Subjects	Outcome
Structural MRI	Schwartz et al. (1997)	19 SAD/19 HC	No change of pituitary volume due to winter depression or season
	Miranda-Scippa et al. (2008)	12 SAD/12 HC	No differences in pituitary volume between SAD and HC
Functional MRI	Vandewalle et al. (2011)	14 SAD/16 HC	Increased response to auditory emotional stimuli in the posterior hypothalamus due to exposure of blue light in SAD
SPECT			
[^{123}I]ß-CIT	Willeit et al. (2000)	11 SAD/11 HC	Decreased [^{123}I]ß-CIT binding in thalamus-hypothalamus in SAD
[^{123}I]ß-CIT	Neumeister et al. (2001)	11 SAD/11 HC	Reduced availability of striatal DAT in patients with SAD
[^{99m}Tc]HMPAO	Praschak-Rieder et al. (1998)		Increased left frontal rCBF in patients with SAD. Normalisation in rCBF after successful light therapy
PET			
[^{18}F]FDG	Cohen et al. (1992)	7 SAD/38 HC	Lower metabolic rates with or without light treatment in SAD
	Goyer et al. (1992)	9 summer SAD/45 HC	Altered glucose metabolism in orbital frontal cortex and left inferior parietal lobule in SAD

MRI magnetic resonance imaging, *SPECT* single photon emission computed tomography, *PET* positron emission tomography, *SAD* seasonal affective disorder, *HC* healthy controls, *DAT* dopamine transporter, *rCBF* regional cerebral blood flow

light treatment. The other three patients were studied during the *on-lights* condition first and after 10 days of discontinuation of light treatment. Light treatment consisted of 2.5 h of 2,500-lux full-spectrum light twice a day (morning between 6 and 9 AM, evening between 6 and 9 PM). Patients with SAD showed lower global metabolic rates under *on-* and *off-lights* condition, suggesting that a lowered metabolic state might be a trait marker of SAD. As suggested by the authors, an alternative explanation for the failure to detect differences in patients during *on-* and *off-light* condition may have been the insufficient length of light therapy. However, light therapy was sufficient to reverse depressive symptoms in these patients.

The second PET study on cerebral glucose metabolism was conducted in patients suffering from summer SAD (Goyer et al. 1992). Nine patients were investigated showing significantly different regional glucose metabolic rates in orbital frontal cortex and in left inferior parietal lobule compared to healthy controls.

In contrast to the small number of studies investigating SAD patients (see Table 8.1), several neuroimaging studies analysing seasonal effects on monoaminergic neurotransmitter systems have been conducted.

As mentioned before, SPECT studies using the non-selective radioligand [^{123}I] ß-CIT revealed contradictory results with respect to seasonal effects on SERT binding (Neumeister et al. 2000; Ruhe et al. 2009). A PET study by Praschak-Rieder et al. conducted in a larger group of healthy drug-naïve subjects ($n = 88$) (Praschak-Rieder

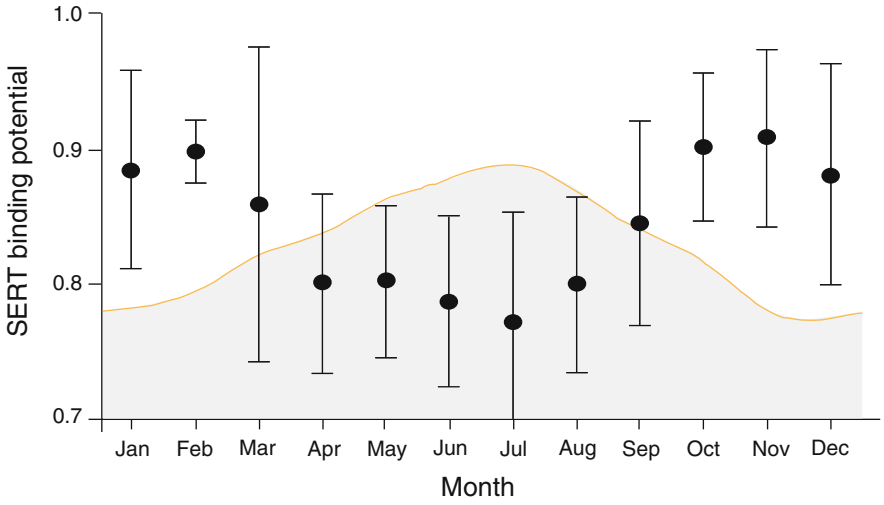

Fig. 8.1 Reciprocal peaks and troughs of serotonin transporter (*SERT*) binding and duration of sunshine in 88 healthy subjects. *Shaded area*: duration of sunshine in Toronto, Ontario (range, between 2.4 and 9.2 h a day. SERT BP_{ND} measured by the selective SERT radioligand [^{11}C]DASB and positron emission tomography. *Circles* represent bimonthly moving averages of mean binding potential values in six predefined regions of interest (prefrontal cortex, anterior cingulate, caudate, putamen, thalamus and midbrain). *X*-axis: calendar months (Modified according to Praschak-Rieder et al. (2012))

et al. 2008) was able to demonstrate a considerable effect of season on SERT by using the specific SERT radioligand [^{11}C]3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile ([^{11}C]DASB) and PET. This study revealed high [^{11}C]DASB binding potential (BP_{ND}) values in autumn and winter in six different predefined regions of interest (ROI). A uniform decrease of regional BP_{ND} values was found in spring and summer (Fig. 8.1). Peak differences in [^{11}C]DASB BP_{ND} values between months with highest and lowest binding potential values as large as 40 %. Furthermore, [^{11}C]DASB BP_{ND} values showed a negative correlation with the duration of daily sunshine and day length. In accordance with this study, Kalbitzer et al. (2010) reported a negative correlation of [^{11}C]DASB BP_{ND} values and daylight minutes. In the latter study, 54 healthy subjects were investigated using [^{11}C]DASB PET and genotyped for a polymorphism in the promoter region of the SERT gene (5-HTTLPR). Only carriers of 5-HTTLPR s-allele showed significant effects of season in [^{11}C]DASB binding. In contrast, 5-HTTLPR l-allele homozygous subjects did not exhibit seasonal variation of SERT availability. The methodology used in both studies does not allow for differentiation between the influence of daily sunshine and the astronomical photoperiod (daylight minutes) on [^{11}C]DASB binding because both parameters are highly intercorrelated. Although the negative correlation between [^{11}C]DASB binding and duration of daylight was found in both studies, a study by Murthy et al. (2010) did not replicate these findings.

Additionally, effects of season on SERT binding were demonstrated by Buchert and colleagues (2006) using PET and the radioligand

trans-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{11}C]-(+)McN5652). This study investigated age-related effects on SERT binding in 29 healthy subjects. In line with the results obtained by [^{11}C]DASB PET, SERT binding measured with [^{11}C]-(+)McN5652 PET was higher in winter, while age did not show any effect on SERT availability in this sample.

In summary, variations in SERT, with higher serotonin transporter availability in times of less light, as shown by the aforementioned studies, may facilitate extracellular serotonin loss during winter, potentially leading to hyposerotonergic symptoms and lower mood. To our knowledge, there are no studies on seasonal variations in SERT binding in patients with SAD. However, the data provided by Ruhe et al. (2009) suggest that there is a similar increase in SERT binding in patients with major depressive disorder in winter.

Recently, a study by Spindelegger et al. (2012) revealed light-dependent alterations of brain serotonin 1A (5-HT$_{1A}$) receptor binding. Among the different subtypes of serotonin receptors, the inhibitory 5-HT$_{1A}$ receptor has a particular role. Located on GABAergic and glutamatergic neurons in limbic and cortical brain regions, the receptor mediates the inhibition of postsynaptic firing (Varnas et al. 2004). In contrast, 5-HT$_{1A}$ receptors located on serotonergic neuronal somatodendrites inhibit serotonergic cell firing and modulate 5-HT transmitter release into the synaptic cleft. Consequently, these 5-HT$_{1A}$ autoreceptors constitute the decisive factor in a negative auto-regulatory loop of serotonin release (Bundgaard et al. 2006). Alterations in 5-HT$_{1A}$ receptor binding have been reported in several neuropsychiatric disorders such as anxiety (Akimova et al. 2009) and depression (Drevets et al. 2007). One recent animal study provided evidence for seasonal alterations in 5-HT$_{1A}$ receptor expression (Naumenko et al. 2008). The study by Spindelegger et al. investigated 36 healthy drug-naïve subjects by quantifying 5-HT$_{1A}$ BP$_{ND}$ using PET and the highly specific ^{11}C-labelled tracer [*N*-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl))-*N*-(2-pyridyl)-cyclohexane-carboxamide] (*carbonyl*-[^{11}C]WAY-100635). Individual exposure to external factors such as global radiation (defined as total of direct solar radiation and diffuse sky radiation received by a unit horizontal surface) correlated with regional 5-HT$_{1A}$ BP$_{ND}$, demonstrating a positive correlation between the accumulated (5 days prior to PET scan) amount of global radiation and 5-HT$_{1A}$ receptor binding. Moreover, this investigation showed a significant difference between the groups of subjects exposed to low versus high amounts of global radiation (see Fig. 8.2). Up to 30 % differences in regional 5-HT$_{1A}$ BP$_{ND}$ were found between the different exposure groups.

In regard to the effects of season on serotonergic neurotransmission, higher SERT availability in times of less light was revealed in four different studies using SPECT and PET. Furthermore, serotonin receptor binding has been shown to be influenced by external factors such as global radiation. However, these results warrant independent replication. Altogether, these findings underline the importance of research in the field of the effects of season on the serotonergic system, as they provide additional insights into regulatory processes in 5-HT neurotransmission. Consequently, future studies investigating serotonergic target structures such as SERT or serotonin receptors should consider seasonal effects.

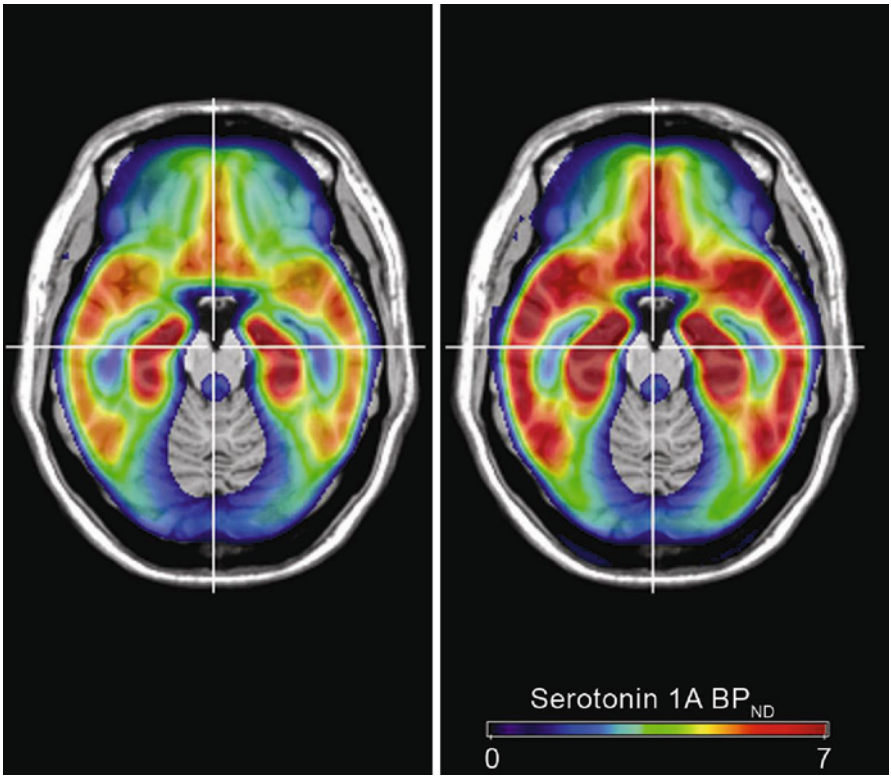

Fig. 8.2 Mean serotonin-1A receptor binding potential (5-HT_{1A} BP_{ND}) in subjects exposed to low amounts of global radiation (*left*) versus subjects exposed to high amounts of global radiation (*right*) showing 5-HT_{1A} BP_{ND} values in the group exposed to a low amount of global radiation, especially in limbic brain regions. Subjects exposed to low amounts of global radiation ($n=22$): 5-day accumulation of global radiation was lower than 8,946 J/cm^2; subjects exposed to high amounts of global radiation ($n=14$): 5-day accumulation of global radiation was higher than 8,946 J/cm^2 (Modified according to Spindelegger et al. (2012))

Dopamine neurotransmission has been suggested to be regulated in part by photoperiodic and light-dependent rhythms. Dopamine is strongly involved in physiological functions such as motor control, cognition, reward, emotion and memory processes (Dalley and Everitt 2009). Limited evidence for seasonal effects on dopamine neurotransmission is provided by SPECT studies mentioned before (Neumeister et al. 2001; Tsai et al. 2011) and a PET study by Eisenberg et al. (2010) reporting higher striatal fluorine-18-L-dihydroxyphenylalanine ([^{18}F]DOPA) uptake in autumn and winter as compared to spring and summer. Eisenberg and colleagues investigated a large sample of healthy subjects ($n=86$) showing higher striatal K_i values in subjects scanned during the fall and winter season. The increased K_i values in the posterior putamen were interpreted as greater presynaptic dopamine synthesis and storage capacity in this region. Based on the resulting higher levels of dopamine in times of less light, these results would be in line with recent findings

of lower striatal [^{123}I]IBZM binding in times of less light exposure (Tsai et al. 2011) due to greater competition at postsynaptic $D_{2/3}$ receptors. Since there is only limited evidence supporting this hypothesis, further investigations are needed to clarify the underlying mechanisms.

8.5 Summary

Seasonal affective disorder and its subsyndromal form constitute a prevalent neuropsychiatric disorder characterised by severe seasonal changes in mood and behaviour. Atypical or reverse vegetative symptoms such as increased sleep duration, hyperphagia and subsequent weight gain are frequent in SAD, and severity of symptoms tends to correlate positively with latitude. During the last decades, only a limited number of studies specifically investigating SAD have been conducted. Apart from brain metabolic changes, monoamine systems in the human brain have been revealed to have a key role in seasonal modulation of behavioural and psychological domains. One of the most consistent findings is the seasonal variation of serotonin transporters with higher availability in winter as shown by four neuroimaging studies using different imaging technologies (Buchert et al. 2006; Kalbitzer et al. 2010; Praschak-Rieder et al. 2008; Ruhe et al. 2009). Other intriguing findings, such as seasonal changes in dopamine neurotransmission (Eisenberg et al. 2010; Tsai et al. 2011) or light-induced alterations in serotonin receptors (Spindelegger et al. 2012), are still awaiting replication. Given the lack of neuroimaging studies in SAD, further research (e.g. seasonal variations in monoamine oxidase activity) is needed to enhance the progress in understanding the molecular background of SAD and seasonal changes in the human brain. Furthermore, knowledge of seasonal effects on brain monoamine function might lead to additional treatment strategies in SAD.

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