

Update on the Biology of Seasonal Affective Disorder

By Chang-Ho Sohn, MD, and Raymond W. Lam, MD, FRCPC

Needs Assessment

A comprehensive review of studies on the pathophysiology of seasonal affective disorder (SAD) was published in 2000. Since then, researchers have documented many new findings that clarify several biological hypotheses in SAD, including studies of circadian rhythms, neurotransmitter function, and molecular genetics. Clinicians will be better able to diagnose and treat patients with SAD by understanding these latest theories of the biology of SAD.

Learning Objectives

At the end of this activity, the participant should be able to:

- Compare and contrast the evidence to support circadian rhythm theories of SAD.
- Describe the data supporting neurotransmitter theories of SAD.
- Summarize the findings from gene association studies of SAD.
- Identify methodological and integrative issues in the biological study of SAD.

Target Audience

Neurologists and psychiatrists

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This activity has been peer-reviewed and approved by Eric Hollander, MD, professor of psychiatry, Mount Sinai School of Medicine. Review Date: June 10, 2005.

To Receive Credit for This Activity

Read this article, and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME quiz found on pages 672 and 673. To obtain credits, you should score 70% or better. Termination date: August 31, 2007. The estimated time to complete this activity is 3 hours.

ABSTRACT

The etiology and pathophysiology of seasonal affective disorder (SAD) has been linked to the seasons and to light since its first conceptualization. Aspects of SAD that make it particularly amenable to biological investigation include the predictable recurrent episodes, the rapid response to a nonpharmacologic treatment, the specific neurovegetative features, and the availability of rich animal models of seasonality. This paper reviews new findings for the major biological hypotheses for SAD, focusing on circadian rhythms, neurotransmitters, and molecular genetics. Integrative issues and future directions for the study of SAD, including the heuristic value of a dual-

vulnerability hypothesis that conceptualizes seasonality as a dimensional construct and the importance of studying endophenotypes, will be discussed.

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INTRODUCTION

All living organisms are influenced by the seasons. The degree of seasonal change in mood and behavior is termed "seasonality"¹ while seasonal affective disorder (SAD) is usually considered to be at the extreme end of the spectrum of seasonality.² In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,³ winter SAD is concep-

Dr. Sohn is clinical fellow at the Mood Disorders Centre at the University of British Columbia Hospital and Vancouver Coastal Health Research Institute, both in Vancouver, British Columbia, Canada. Dr. Lam is professor in the Department of Psychiatry, head of the Department of Psychiatry's Division of Clinical Neuroscience, and director of the Mood Disorders Centre at the University of British Columbia.

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Please direct all correspondence to: Raymond Lam, MD, FRCPC, Division of Clinical Neuroscience, Department of Psychiatry, University of British Columbia, 2255 Westbrook Mall, Vancouver, BC, Canada V6T 2A1; Tel: 604-822-7325, Fax: 604-822-7922; E-mail: r.lam@ubc.ca.

tualized as a seasonal pattern of recurrent major depressive episodes during the fall/winter in the absence of seasonal psychosocial stressors, with full remission of symptoms in spring/summer. This seasonal pattern can be applied to both unipolar major depressive disorder (MDD) and bipolar disorder.

Based on DSM criteria, the prevalence of SAD in epidemiological studies has been estimated at 0.8% to 2.8% in North America,^{4,5} but the prevalence of significant seasonality (or “subsyndromal SAD”) is likely much higher, with estimates of 15% to 25% in the global population.⁶ In addition to seasonality, SAD has two prominent characteristics: so-called atypical depressive symptoms and responsiveness to light treatment. Most patients with SAD experience atypical symptoms including increased need for sleep, carbohydrate craving with increased appetite and weight, and extreme fatigue. These symptoms, which are similar to seasonal changes in behavior shown by many mammals in response to winter, might be a human expression of a basic evolutionary process to achieve maximum conservation of energy during winter.⁷ The other important characteristic of SAD is the response to exposure to bright light, known as light therapy or phototherapy.

There are four specific aspects to SAD that make it particularly of interest for biological investigation. The first is the seasonality of the condition. The predictable onset and offset of winter episodes allow the investigation of biological parameters at different stages of the disorder, from acute illness to natural remission and vice versa. The second aspect is the rapid response to light therapy. This nonpharmacologic treatment allows comparison of the treated state to the natural, untreated summer remission state. The third aspect is the specificity of the neurovegetative symptoms of SAD (eg, extreme fatigue, hypersomnia, and increased appetite). These symptoms contrast to those of other types of mood disorders (eg, melancholic depression) and may be especially important when comparing SAD to other psychiatric conditions in which similar symptoms are prominent, such as atypical depression and certain sleep and eating disorders. Finally, there is a rich abundance of animal models of seasonality to develop and test specific biological hypotheses about SAD.

In 2000, Lam and Levitan⁸ comprehensively reviewed the pathophysiology of SAD focusing on evidence for and against the major hypotheses: circadian rhythms, neurotransmitter function, and genetics. In the current article, we update the review

with new data from the past 5 years of studies of SAD and its response to light therapy. We also highlight some important integrative issues and future directions for the study of SAD and seasonality.

CIRCADIAN RHYTHMS

In humans, the central pacemaker that entrains internal circadian rhythms to synchronize with external time cues (zeitgebers) is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Light, the most powerful zeitgeber, is conveyed to the SCN through the eyes via the retinohypothalamic tract. A complex neural pathway links the SCN to the pineal gland, where melatonin is secreted under influence of both the SCN (a circadian mechanism) and external light exposure (a direct suppression effect). In many animals, melatonin is a mediating hormone between light and seasonal behavior.

Melatonin displays a robust circadian rhythm with high levels secreted at night and low plasma levels present during the day. The circadian rhythm phase of melatonin can be described by the usual time at which the melatonin level begins to rise at night, usually around 8:00 PM, collected under dim light conditions to prevent any direct suppressant effects of light exposure. This is known as the dim light melatonin onset (DLMO).

Light can predictably shift circadian rhythms, with the direction and magnitude of phase shift dependent on when the light exposure occurs in the circadian cycle. For example, bright light exposure in the late evening can delay the circadian rhythm of melatonin (ie, the DLMO occurs at a later time each day, such as 10:00 PM), while morning light exposure results in phase advance of the melatonin rhythm (ie, the DLMO occurs at an earlier time than usual, such as 8:00 PM) (Figure 1). The phase shift of one circadian rhythm (eg, melatonin) can change the time interval to another circadian rhythm (eg, sleep-wake cycle), the so-called phase angle. Figure 1 illustrates an example of phase shift of DLMO causing a change in phase angle with waking time.

Circadian rhythm theories,² including photoperiod and phase-shift hypotheses, initiated the study of SAD and the use of light treatment in depression and other psychiatric conditions. These hypotheses remain prominent in the pathophysiology of SAD and seasonality, but there are also other recent circadian findings in SAD,^{9,10} such as disturbances in thermoregulation and electroencephalographic slow-wave sleep.

Photoperiod Hypothesis

Rosenthal and colleagues² first suggested that the shorter winter photoperiod (light/dark cycle) might induce depression. There have been three lines of investigation to verify the photoperiod theory.¹¹ The first involves studies correlating the prevalence of SAD with increasing latitude, since photoperiod is directly influenced by latitude (eg, the winter days are shorter at more northerly latitudes). The results of numerous epidemiological studies have been inconsistent, in part due to methodological limitations of the various studies. The most rigorous studies^{4,11} did not find correlations of prevalence of SAD with latitude, although the range of latitude studied was small. Reviews^{6,12} summarizing the more methodologically sound studies have shown that there does appear to be a relationship between SAD and latitude, but this effect is complex and relatively weak.

Since melatonin is only secreted in the dark, the duration of melatonin secretion acts as a signal for photoperiod for many mammalian circadian systems.¹³ Previous studies⁸ of melatonin as a hormonal indicator of photoperiod showed conflicting results in SAD. Recently, Wehr and colleagues¹⁴ measured the duration of melatonin secretion in constant dim light in 55 patients with SAD and matched healthy control subjects. While there were no significant differences in the duration of melatonin secretion between the two groups in winter, the patients with SAD had a significant seasonal variation with longer melatonin duration in winter than in summer. This suggests that only people with SAD respond to photoperiod in a manner similar to other mammals, while healthy people seem to have lost this seasonal time signal. Potential mechanisms to explain this finding include seasonal differences in the experience of natural or artificial light exposure,^{15,16} differences in retinal sensitivity to light,¹⁷⁻¹⁹ or differences within the neural pathways of the circadian system (eg, abnormal clock genes).

The third line of investigation involves the mechanism of light treatment, specifically whether photoperiod extension by artificial light is necessary to treat SAD.² One meta-analysis²⁰ of light therapy studies found that morning-plus-evening light (a photoperiod extension schedule) was superior to single exposures at other times of the day. Other meta-analyses,²¹⁻²³ however, indicate that morning light exposure is superior to evening light, which initially seems to refute the photoperiod extension hypothesis. An alternative interpretation is that morning light may still act to extend the photoperiod by truncating early morning melatonin secretion and reducing the overall melatonin duration.

Phase-Shift Hypothesis

In contrast to photoperiod, the phase-shift hypothesis as first proposed by Lewy and colleagues²⁴ states that SAD results from internal circadian rhythms that are phase delayed relative to the external clock or to other rhythms, such as the sleep-wake cycle. According to this hypothesis, light therapy exerts its effect by correcting the abnormal phase delay. Morning light exposure that results in phase advance of circadian rhythms should therefore show superior effectiveness to that of evening light, which induces a further phase delay.

The phase-delay hypothesis has proven to be one of the most robust theories of SAD, but also, because of some conflicting findings, the most controversial. In part, this is due to the difficulty in studying circadian rhythms in humans due to masking effects of external zeitgebers including light exposure, sleep, and activity. As previously reviewed,⁸ no phase differences were observed in patients with SAD in 24-hour rhythms of melatonin, cortisol, prolactin, thyrotropin, and body temperature,²⁵⁻²⁷ although these rhythms may be influenced by masking effects. Studies²⁸⁻³¹ using the DLMO, a marker of circadian phase that is relatively

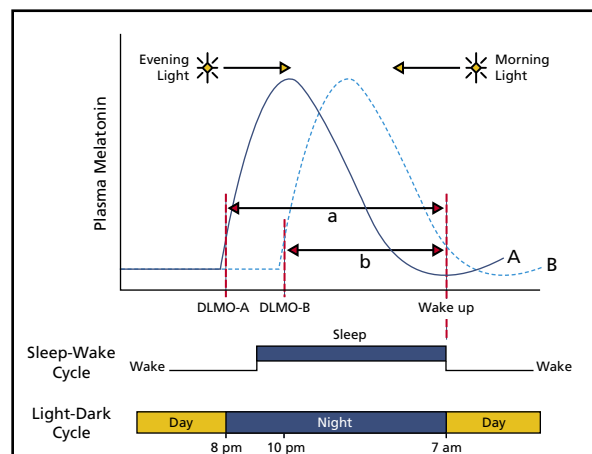


FIGURE 1. Schematic diagram of circadian rhythms of melatonin and sleep-wake cycles*

* Phase of the melatonin cycle (A) is represented by DLMO-A, while the phase of the sleep-wake cycle is represented by the wake-up time. The phase angle between the melatonin and sleep-wake cycles is represented by the time interval between DLMO-A and wake-up time (a). Light exposure in evening results in a phase delay of the melatonin rhythm (B), as measured by DLMO-B. If wake-up time remains constant, then the phase-delayed melatonin rhythm results in a smaller phase angle with the sleep-wake cycle (b). A phase-delayed rhythm can be corrected using morning light exposure, which causes a phase-advance of circadian rhythms.

DLMO-A=dim light melatonin onset for melatonin rhythm A; DLMO-B=dim light melatonin onset for melatonin rhythm B.

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free from masking effects,²⁸ have more consistently found evidence for phase delays in SAD.²⁹⁻³¹

Other studies using specific techniques to study endogenous circadian rhythms in SAD have had mostly negative results.³⁰⁻³⁵ In studies using constant routine protocols that rigorously control for masking effects, one study³² found phase delays in body temperature, DLMO, and cortisol rhythms in 6 female patients with hypersomnic SAD studied in winter, while the other did not find any significant phase differences.³³ Forced desynchrony studies,^{34,35} in which 20-hour sleep-wake cycles are imposed on subjects thereby unmasking the endogenous circadian rhythm, also found no differences in 7 patients with SAD compared with controls studied in winter and summer. However, one patient did show significant phase-delayed circadian rhythms,³⁶ suggesting that there may be inter-individual variation in SAD. Given that examining endogenous circadian rhythms requires technically demanding and/or resource-intensive methods, only small numbers of patients are usually studied. Hence, patient selection is particularly important in these small-sample studies and may explain some of the negative findings.

Similarly, there have been conflicting results in the effects of light therapy on phase changes in SAD. The phase-shift theory rests on two necessary components of treatment—that a corrective phase advance of circadian rhythms should occur and that the phase advance should be correlated with the antidepressant effect. In support of the first component, most studies and meta-analyses²¹⁻²³ have shown that morning light exposure results in the phase advance of circadian rhythms and is more effective than light at other times of the day. However, there are conflicting results for the second component: a correlation between the phase advance and antidepressant effect.^{31,32,37,38} For example, some previous studies³¹ have found that clinical improvement was correlated with degree of phase advance while others have not.^{32,37,38}

Recent light therapy studies,³⁹ however, have provided more evidence to support the phase-shift hypothesis. Terman and colleagues³⁹ sampled the DLMO in 42 patients with SAD before and after light therapy. They found that the magnitude of phase shifts depended on the phase angle from the DLMO to the time of light exposure, with responses to morning light increasing with the size of the phase advance. An optimal time for administration of morning light was found to be 8.5 hours after the DLMO or 2.5 hours from the midpoint of sleep duration.

Another study⁴⁰ involved 26 patients with SAD who had rectal core body temperature monitoring

during a light therapy protocol. In this study, the degree of phase advance in core body temperature was only weakly correlated with antidepressant response, although there appeared to be an optimal phase angle for response occurring when the wake time was ~3 hours from the nocturnal temperature minima.

Melatonin, administered at an appropriate time in the evening to achieve a circadian phase-advance, can also be used to examine the phase-shift hypothesis. A pilot study⁴¹ showed that low-dose melatonin administered in the evening was effective in SAD, but a subsequent larger study (N=100 patients with SAD)⁴² found no overall treatment differences between morning and evening dosing of melatonin and a placebo pill condition. However, a post hoc analysis⁴² showed that the patients who were most phase delayed at baseline responded to a corrective phase advance by melatonin and that the best responses occurred when patients achieved an optimal phase angle in which the DLMO occurred ~14 hours from wake time.⁴²

In summary, there is substantial evidence to support that some, but not all, patients with SAD have phase-delayed circadian rhythms that can be corrected by appropriately timed circadian interventions (melatonin or bright light exposure) with resultant improvement in depressive symptoms. However, there is also evidence indicating that other people with SAD have beneficial effects of light therapy independent of circadian phase-shifting effect.

NEUROTRANSMITTERS

Since SAD is a subtype of major depression, there has been much interest in studying the major neurotransmitters of interest in depression, namely serotonin (5-HT), noradrenaline, and dopamine. There has been special interest in 5-HT, given the abundant evidence that seasonal variation of brain and peripheral 5-HT occurs in healthy people. For example, recent studies found that both 5-HT turnover⁴³ and availability of hypothalamic 5-HT transporter sites, as measured by single photon emission computed tomography,⁴⁴ are lower in winter than in summer.

In SAD, past studies⁸ of metabolites of 5-HT and catecholamines in peripheral blood and cerebrospinal fluid were inconclusive. More consistent results were found in neuroendocrine challenge studies, in which blood levels of hormones are measured after administering a drug that acts on specific receptors that control secretion of that hormone. Studies using primarily serotonergic drugs acting on various 5-HT receptors consistently showed evidence for serotonergic receptor dysfunction in

SAD.⁴⁵ However, there are problems with interpreting the results of neuroendocrine challenge studies. For example, they are only indirect measures of brain function since they involve the pituitary gland which is outside the blood-brain-barrier. Also, they only provide correlative measures, since there is no way to determine whether any receptor dysfunction is directly related to SAD symptoms, or whether they are merely epiphenomena of the illness.

More recent investigations focus on monoamine depletion protocols in which brain monoamines can be experimentally manipulated to determine whether changes lead to depressive symptoms, thereby giving a more direct means of linking neurotransmitter function to behavior.⁴⁶ For example, tryptophan depletion studies are conducted on the understanding that tryptophan is the dietary amino acid precursor for conversion to 5-HT in the brain. When a mixture containing large amounts of amino acids without tryptophan is ingested, the ensuing increase in liver enzyme metabolism can temporarily reduce the blood levels of free tryptophan by $\geq 80\%$ within 5 hours. Animal studies and neuroimaging studies in humans show that brain 5-HT is reduced by a similar magnitude using this procedure.^{47,48} This technique has been widely used in studies investigating mechanisms of antidepressant action and the neurobiology of nonseasonal depression.^{49,50}

In the study of untreated, symptomatic patients with SAD,⁵¹ tryptophan depletion did not exacerbate the depressive symptoms in winter, similar to findings in nonseasonal depression. However, in patients with SAD in short-term clinical remission with light therapy, Lam and colleagues⁵² first reported that tryptophan depletion induced relapse of depressive symptoms, thereby reversing the effect of light therapy, a finding subsequently replicated by two independent groups.^{53,54} Interestingly, atypical symptoms like carbohydrate craving were most sensitive to the tryptophan depletion protocol, implicating the role of 5-HT in the development of these symptoms. During the natural summer remitted state, tryptophan depletion studies produced mixed findings; two studies^{55,56} reported significant relapse of symptoms while another⁵⁷ did not. A preliminary report⁵⁸ also found that patients with SAD who showed relapse with tryptophan depletion in summer were more likely to experience a depressive episode in the following winter, suggesting that tryptophan depletion may predict risk for SAD.

Similarly, depletion of brain catecholamines can be accomplished using α -methyl-para-tyrosine (AMPT), an inhibitor of tyrosine hydroxylase that decreases synthesis of dopamine and noradrenaline.^{46,59,60} In a study by Neumeister and colleagues,⁵⁴

tryptophan depletion and catecholamine depletion each induced relapse of symptoms in patients with SAD in remission with light treatment, indicating that light therapy may act through several neurotransmitters. Patients in summer remission also showed robust relapses with catecholamine depletion, suggesting that dopamine and/or noradrenaline dysfunction is directly involved in the pathogenesis of winter depression.⁶¹ Of note in this regard is that reboxetine (a selective inhibitor of noradrenaline reuptake) and bupropion (an inhibitor of noradrenaline and possibly dopamine reuptake) may be beneficial treatments for SAD.^{62,63}

Other studies^{19,64,65} also support dopamine involvement in SAD. Electroretinography (ERG) is a method to assess retinal function in light- and dark-adapted states that involves dopamine as the mediating neurotransmitter. ERG studies¹⁹ found evidence of reduced b-wave amplitude consistent with decreased retinal dopaminergic activity in SAD. A neuroimaging study⁶⁴ using [¹²³I]β-carbomethoxy-3beta-(4-iodophenyl) tropane single-photon emission computed tomography showed decreased availability of striatal dopamine transporter binding sites in symptomatic patients, although another similar study also found evidence of reduced brain 5-HT transporter sites in patients with SAD.⁶⁵

GENETICS

Much of the recent activity in the biological investigation of SAD has involved the pursuit of genetic mechanisms through different approaches including family studies, twin studies, and candidate gene association studies.⁶⁶⁻⁷⁴ provided evidence for hereditary factors in both SAD and seasonality (Table 1). In family history studies,⁶⁶⁻⁷⁰ 25% to 67% of patients with SAD had a positive family history of affective illness while 13% to 17% had first-degree relatives with SAD. These rates are significantly higher than expected from population prevalence studies.⁷¹ However, no significant differences in psychiatric disorders among first-degree relatives were found in patients with SAD compared with those with nonseasonal depression.^{66,72}

Although there are no twin studies involving SAD, per se, there have been two studies of seasonality (Table 1).^{73,74} In Australia, Madden and colleagues⁷³ conducted volunteer-based twin studies with 4,639 adult twins and reported that genetic effects accounted for 29% of variance in seasonality scores. A similar twin study in Canada^{74,75} found greater heritability for seasonality scores, accounting for 45% to 69% of the total variance, perhaps because the phe-

notypic expression of seasonality is greater at higher latitudes. These and the family history findings indicate that SAD and seasonality has robust heritability. Of course, signals from family history and twin studies must be further investigated using molecular genetic analyses, which has been the most active area for SAD research in the past 5 years. Formal genetic linkage studies for complex conditions, such as SAD, are limited by low power and poor feasibility, therefore, the focus has been on case-control association studies of candidate genes (Table 2).

Obvious candidate genes include genes involved in the 5-HT system. Several studies⁷⁷⁻⁸¹ examined the 5-HT transporter promoter repeat length polymorphism (5-HTTLPR) after Rosenthal and colleagues⁷⁷ and Sher and colleagues⁷⁸ first reported that the short variant allele of the 5-HTTLPR was associated with

SAD and seasonality. Unfortunately, other studies^{79,80} could not replicate this finding. Johansson and colleagues⁸¹ subsequently conducted a pooled analysis of all three studies (including the original sample) that also failed to find an association between 5-HTTLPR and SAD. However, that report did show a difference in 5-HTTLPR genotypes between high and low seasonality groups in a separate population-based sample.⁸¹

There are several reports of positive findings with the 5-HT_{2A} gene, including increases in the frequency of the 102C allele⁸² and the -1438A allele of the 5-HT_{2A} gene,⁸³ and an association of the 102T/C genotype with childhood attention deficit disorder.⁸⁴ However, there are also negative studies involving 5-HT_{2A} genes^{79,85} and other 5-HT-related genes (Table 2).⁷³

It may be more worthwhile to investigate the

TABLE 1. FAMILY HISTORY AND TWIN STUDIES IN SAD

Author(s) (Year)	Type of Study	Sample	Results
Rosenthal et al ⁷⁵ (1986)	Family history	7 children with SAD	5 of 7 children with SAD had a parent with SAD.
Thompson et al ⁷⁰ (1988)	Family history	51 patients with SAD	25% and 14% of SAD patients had a positive history in first-degree relatives of affective illness and SAD, respectively.
Lam ⁶⁸ (1989)	Family history	46 patients with SAD	64% and 13% of SAD patients had a positive history in first-degree relatives of affective illness and SAD, respectively.
White et al ⁶⁹ (1990)	Family history	61 patients with SAD	66% of SAD patients had family members with nonseasonal depression, SAD or alcohol abuse.
Allen et al ⁶⁶ (1993)	Family history	34 patients with SAD; 34 matched nonseasonal depressed patients	27% of SAD patients had first-degree relatives with mood disorders. No differences were found in family histories between SAD and nonseasonal depression.
Sasaki et al ⁷⁶ (1998)	Family history	129 small families from the general population in Japan	No association between children and biological parents in seasonal changes of sleep and eating behaviour.
Stamenkovic et al ⁷² (2001)	Family history	36 patients with SAD; 36 matched nonseasonal depressed patients	No differences in the lifetime prevalence for psychiatric disorders among the first-degree relatives in both groups (SAD=16.5% and nonseasonal depression=19%).
Madden et al ⁷³ (1996)	Twin	4,639 adult twins from a volunteer-based registry in Australia	Genetic effects accounted for at least 29% of the variance in seasonality scores.
Jang et al ⁷⁴ (1997)	Twin	339 adult twins from a volunteer-based registry in Canada	Genetic effects in men and women accounted for 69% and 45% of the variance in seasonality scores, respectively.

SAD=seasonal affective disorder.

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genetics of specific endophenotypes of SAD.⁸⁶ For example, differences in 5-HTTLPR have been associated with comorbid premenstrual depressive disorder⁸⁷ and self-directedness scores on personality testing⁸⁸ in some patients with SAD. Furthermore, Levitan and colleagues⁸⁹ studied a putative endophenotype of SAD, women with carbohydrate craving and hyperphagia or binge-eating, and its relationship with the 7R allele of the D4 dopamine receptor gene (DRD4). The 7R allele was not associated with the diagnosis of SAD, per se, but instead was associated with a history of childhood attention-deficit disorder and higher body mass index;⁸⁹ moreover, this association appeared to be mediated through binge eating behavior.⁹⁰

Another candidate gene comes from the guanine nucleotide-binding (G-protein) system that is involved in postsynaptic signal transduction and which has been of significant interest in nonseasonal depression.⁹¹ There is some evidence for G-protein dysfunction in SAD, as one study⁹² found that patients with SAD had decreased levels of G β -subunit in peripheral leukocytes. A single nucleotide polymorphism (C825T) in the G β 3-subunit gene has been shown to influence intracellular response to G-protein-coupled stimuli⁹³ and an association of the T allele with nonseasonal affective disorder has been reported.⁹⁴ In SAD, one study⁹⁵ found that patients were more likely than control subjects to carry the T allele of the G β 3-subunit gene polymorphism, but there was no association of the polymorphism with seasonality scores. Unfortunately, another study⁹⁶ did not replicate these findings.

Circadian clock genes are also of significant interest given the prominence of circadian rhythm hypotheses for SAD. In animal studies, mutations in clock and period genes result in altered circadian rhythms.⁹⁷⁻⁹⁹ Johansson and colleagues⁸¹ conducted a study for potential association between polymorphisms in clock-related genes (clock, period2, period3, and NPAS2) and SAD, seasonality and diurnal preference. They found a significant difference between patients with SAD and control subjects in NPAS2 471 Leu/Ser, indicating a recessive effect of the leucine allele on disease susceptibility.¹⁰⁰ Period3 647 Val/Gly was also associated with scores on self-reported morningness-eveningness (a measure of diurnal preference) with higher scores found in individuals with at least one glycine allele. However, none of the polymorphisms in this study were associated with seasonality in the SAD case-control material.

In summary, there are a number of positive findings in gene association studies involving sero-

tonin-, dopamine-, G-protein- and clock-related genes. Association studies are susceptible to false positive results, so replication of these results will be important. For example, initial enthusiasm for an abnormality in 5-HTTLPR was not confirmed in subsequent pooled analyses.

INTEGRATIVE ISSUES AND FUTURE DIRECTIONS

There has been considerable progress in studying the biology of SAD, but many findings require replication and there continue to be conflicting results that need to be explained. It is now widely recognized that there must be heterogeneity in SAD similar to that seen in nonseasonal depression. One possibility is that the clinical presentation of SAD represents a final common pathway with multiple etiologies that contribute to heterogeneity when examining groups of patients. This may be especially true for circadian hypotheses, since there is great interindividual variability in circadian phase position and phase shifts produced by circadian interventions. Hence, averaging group data, especially in small-sample studies, may not reflect the endogenous circadian rhythms in a subset of subjects. Similarly, circadian treatments given at the same clock time may produce very different phase-changes between individuals, depending on their starting circadian phase at baseline.

Another explanation for this heterogeneity may be related to the inadequacies of the current definition of SAD as a subtype of depression. Considering seasonality as a dimensional construct instead of a categorical diagnosis may be more informative in understanding biological mechanisms. In this regard, a dual-vulnerability hypothesis, first proposed by Young and colleagues¹⁰¹ and subsequently extended by Lam and colleagues,¹⁰² posits distinct factors associated with seasonality and depression. Differential loading of each factor within an individual may explain some of the different presentations of seasonality. For example, a person with high loadings on a seasonality factor coupled with moderate loadings on a depression factor may present as having SAD, whereas someone with low seasonality and high depression may present with a nonseasonal depressive episode.¹⁰² Other differences in loading on the two factors may result in different clinical presentations such as subsyndromal SAD (high seasonality, low depression) and "seasonal" MDD (ie, winter worsening of nonseasonal MDD [high seasonality, high depression]).

There may be separate biological mechanisms involved with each factor so that, for example, the

seasonality factor may be due to an underlying circadian disturbance while the depression factor may be caused by serotonergic or dopaminergic dysfunction

(or, as proposed by Young and colleagues,¹⁰¹ by cognitive distortions). Since patients with SAD may have different loadings of the two factors, some

TABLE 2. GENETIC ASSOCIATION STUDIES IN SAD

Author(s) (Year)	Gene Studied (Polymorphism)	Sample	Results
Ozaki et al ⁸⁴ (1996)	5-HT _{2A} (T102C, Ala447Val, C516T)	50 patients with SAD; 62 control subjects	No associations found.
Enoch et al ⁸² (1999)	5-HT _{2A} (-1438G/A)	67 patients with SAD; 69 control subjects	Increase in frequency of the -1438A allele in patients with SAD; No association between -1438G/A and seasonality scores.
Arias et al ⁸¹ (2001)	5-HT _{2A} (T102C)	159 patients with SAD and nonseasonal depression; 164 control subjects	Genotype distributions were different between SAD and nonseasonal depressed patients; 102C-allele carriers were more frequent in the patients with SAD.
Levitan et al ⁸³ (2002)	5-HT _{2A} (T102C)	66 women with SAD	T102C genotypes associated with childhood attention-deficit disorder.
Sher et al ⁷¹ (1999)	5-HT _{1A} (Gly22Ser, Ile28Val), 5-HT _{1D} (T1350C), 5-HT _{1B} (C861G), 5-HT _{1E} (C531T), 5-HT _{2C} (Cys23Ser)	74 patients with SAD; 80 control subjects	No associations found.
Han et al ¹⁰³ (1999)	TPH (T1095C)	72 patients with SAD; other patients with psychiatric disorders	No associations found.
Lenzinger et al ¹⁰⁴ (1999)	5-HTT gene	18 patients with SAD; matched control subjects	No differences genotypes in patients with SAD; no correlation with depression scores after tryptophan depletion.
Rosenthal et al ⁷⁷ (1998)	5-HTTLPR (long/short)	97 patients with SAD; 71 control subjects with low seasonality scores.	5-HTTLPR short allele was more prevalent among patients with SAD.
Sher et al ⁷⁸ (1999)	5-HTTLPR (long/short)	209 healthy subjects	5-HTTLPR short allele associated with higher seasonality scores.
Johansson et al ⁷⁹ (2001)	5-HTTLPR (long/short), 5-HT _{2A} (-1438G/A, 45His/Tyr), 5-HT _{2C} (23Cys/Ser), TRH (218A/C), White (2457G/A)	82 patients with SAD; 82 matched control subjects	No associations with SAD or seasonality and the genotypes of these genes.
Praschak-Reider et al ⁸⁷ (2002)	5-HTTLPR (long/short)	44 women with SAD and PMDD; 43 women with SAD without PMDD	Long/short allele-heterozygosity was associated with presence of PMDD in patients with SAD.
Willeit et al ⁸⁰ (2003)	5-HTTLPR (long/short)	138 patients with SAD; 146 control subjects with low seasonality	No difference in genotype distribution and short allele frequency in patients with SAD. Melancholic depression was associated with the long allele and atypical depression with the short allele

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circadian and neurotransmitter studies may show positive results while others may not. Studying the phenomena of seasonality and subsyndromal variants may thus be informative for SAD. For example, some investigators¹⁰⁵ have shown that seasonality (ie, lowering of mood in winter) is associated with circadian phase delay and that subsyndromal SAD is associated with changes in retinal light sensitivity on ERG,¹⁰⁶ similar to findings in patients with SAD.

A major advantage of studying seasonality is in the multitude of animal models available to

study seasonal changes in behavior. An example of capitalizing on an animal model is the study of neuroimmune function. There is substantial evidence from animal studies¹⁰⁷ showing that melatonin mediates seasonal changes in the immune system and seasonal variations in immune function have also been reported in humans.^{108,109} Other studies¹¹⁰ indicate that (nonseasonal) depression and immune function can influence each other bi-directionally via inflammatory cytokines. Thus, it is possible that the symptoms of SAD result from

TABLE 2. GENETIC ASSOCIATION STUDIES IN SAD (continued from page 642)

Author(s) (Year)	Gene Studied (Polymorphism)	Sample	Results
Johansson et al ⁸¹ (2003)	5-HTTLPR (long/short)	Pooled analysis: 464 patients with SAD; 414 control subjects; 226 individuals from a population-based registry; 46 patients with nonseasonal depression.	Pooled data from previous 3 case-control studies ^{74,77,76} includes new sample of 147 patients with SAD and 115 control subjects. No association between 5-HTTLPR and SAD was found in the new case-control material or in the pooled analysis of all samples. A difference in 5-HTTLPR was detected between the population-based high and low seasonality groups, when assuming a recessive effect of the short allele.
Thierry et al ⁸⁸ (2004)	5-HTTLPR (long/short)	56 female patients with SAD; 76 age-matched control subjects	Patients with SAD carrying the short allele had lower Self-Directedness scores on personality testing.
Levitan et al ⁸⁹ (2004)	DRD4 (7R allele)	108 female patients with SAD with increased eating behavior	7R allele was associated with childhood attention deficit disorder symptomatology and higher maximal lifetime body mass index in patients with SAD.
Levitan et al ⁸⁸ (2004)	DRD4 (7R allele)	131 female patients with SAD with increased eating behavior	7R allele was associated with greater frequency of binge-eaters in patients with SAD.
Willeit et al ⁹⁵ (2003)	Gβ3 (C825T)	172 patients with SAD; 143 control subjects	Increase in frequency of the C825T-allele in patients with SAD. The polymorphism was not associated with seasonality.
Johansson et al ⁹⁶ (2004)	Gβ3 (C825T)	159 patients with SAD; 159 matched control subjects	No association between C825T and SAD or seasonality. Some evidence for an effect on diurnal preference but only in a subset (N=92) of the control group.
Johansson et al ⁸¹ (2003)	Clock, period 2, period 3 (647 Val/Gly), NPAS2 (471 Leu/Ser)	159 patients with SAD; matched control subjects	NPAS2 471 Leu/Ser was associated with SAD and Period3 647 Val/Gly was associated with diurnal preference.

SAD=seasonal affective disorder; 5-HT=serotonin; Ala=alanine; Val=valine; Gly=glycine; Ser=serine; Ile=isoleucine; Cys=cysteine; TPH=tryptophan hydroxylase; 5-HTT=serotonin transporter; 5-HTTLPR=serotonin transporter promoter polymorphism; His=histidine; Tyr=tyrosine; TRH=thyroid releasing hormone; PMDD=premenstrual dysphoric disorder; DRD4=D4 dopamine receptor; Gβ3=G-protein β3 subunit; NPAS2=neuronal PAS domain protein 2; Leu=Leucine;

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the seasonal activation of cytokines in anticipation of winter stress.¹¹¹ Preliminary studies¹¹² have shown that people with SAD had significantly higher plasma levels of cytokine interleukin (IL)-6 and a trend to higher soluble IL-2 receptor levels than control subjects. Tryptophan and catecholamine depletion of patients in remission with light therapy also found that changes in cytokine soluble IL-4 correlated with increase in depressive symptoms.¹¹³ Further investigation of the role of cytokines and neuroimmune function in SAD and seasonality will be of interest.

Another method to reduce heterogeneity is to study more specific endophenotypes of SAD, such as patients with distinct neurovegetative features or comorbidity. It may also be possible to link some of these endophenotypes to other psychiatric conditions via common neurophysiological mechanisms, such as modeling differences in 5-HT_{2A} and DR_{D4} gene polymorphisms to the appetite and attention disturbances found in women with SAD and bulimia nervosa.⁸⁵

Progress in research on mechanisms of circadian regulation will also likely provide clues for research in SAD and seasonality. For example, several studies^{19,106,114} have found evidence for electrophysiological changes in retinal light sensitivity in SAD, but most of these changes reflect rod and cone photoreceptor function. Recent research¹¹⁵⁻¹¹⁷ has shown that photic input to the circadian system is mediated through a separate pathway from that of the visual system, and that traditional visual photoreceptors (eg, rods and cones) are not involved in the transduction of circadian light signals. Instead, novel photopigments, such as melanopsin^{115,117} and cryptochrome,¹¹⁶ have been implicated as circadian photoreceptors. Based on these new findings, research on melanopsin and other circadian photopigments will be of great interest in SAD.

Finally, it is also recognized that the different hypotheses proposed for SAD may not be mutually exclusive. For example, 5-HT can modulate photic response to the SCN and sleep disturbances due to abnormal circadian rhythms may be mediated through serotonergic pathways that depend on postsynaptic G-protein signal transduction. An integrative approach involving circadian rhythms, neurotransmitters and genetics will be more likely to explain the biology of SAD than a single, reductionist approach **CNS**

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