



“Abnormal fluctuations of melatonin, a brain chemical that regulates sleep cycles and related mood and behavior changes, may explain seasonal affective disorder.”

Seasonal Affective Disorder: *Shedding Light on Seasons and the Brain*

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Long nights, gray days, and slushy streets—it’s no wonder January gives everyone the blues. People have known for centuries that mood and behavior can vary with the seasons and that many people’s emotions take a turn for the worst when it seems as if the sun has barely risen before it sets again. However, for between 1.2 percent to as much as 9.7 percent of the population, winter is more than just glum (1, 2). It’s SAD.

SAD, or Seasonal Affective Disorder, is a recurrent psychiatric depression that cycles with the seasons, with episodes of depression most commonly occurring in the fall and winter. Since Rosenthal and associates first described and named the syndrome in 1984 (3), scientists have uncovered much about the biochemical and genetic bases for SAD, and have even developed light therapy treatments to simulate the earth’s natural daily cycles. Yet winter depression is nothing new. As early as 400 BCE, the ancient Greek founder of medicine Hippocrates observed seasonal patterns in depression (5). 2,400 years later, Norman Rosenthal and Thomas Wehr coined the term “Seasonal Affective Disorder” to describe “a condition where depressions

in fall and winter alternate with non-depressed periods in the spring and summer” (2). The DSM-IV, the fundamental diagnostic manual of mental disorders, currently lists SAD as a “specifier” of seasonal symptoms in either bipolar or recurrent major depressive disorders (1).

SAD is comprised of a suite of symptoms, many of which may seem like severe versions of normal winter mood and behavior changes. For example, even healthy people tend to feel drowsier during the winter and tend to eat more, gravitating especially towards carbohydrates and sweets like chocolate (contributing to the much-maligned winter weight gain). However, SAD can also include more life-changing symptoms such as depression, increased sleep, decreased activity, and loss of sex drive, as well as feelings of anxiety, irritability, poor concentration, and social withdrawal (4,6).

The Brain and SAD

Fundamentally, sufferers of SAD experience seasonal variations in their biological rhythms to a much greater extent than people without SAD. Studying the seasonal regulation of

behavior in non-human mammals by means of the circadian pacemaker is one way scientists gain greater understanding of the mechanisms for these seasonal changes. This research explains the biology of SAD in terms of the neural and neurochemical systems that regulate the brain.

Many mammals have neural circuits that respond to daily and seasonal changes in light levels and vary the body’s chemistry and behavior accordingly; these circuits are regulated by a brain region called the circadian pacemaker. Over time, the body establishes a regular internal cycle of day and night and the eye detects changing light intensity in the environment to vary this cycle with the seasons. Every day as dawn approaches, the neurons or nerve cells of the circadian pacemaker rapidly increase their “firing rate,” sending out neurological signals that act like an internal alarm clock that continues going off all day long. These signals inhibit the pineal gland’s release of melatonin, a hormone causing drowsiness. Melatonin secretion decreases at dawn, affecting everything from appetite to reproduction. At dusk, the process reverses, the circadian pacemaker neurons reduce their firing, melatonin lev-

els increase, and the animal sleeps.

Though this melatonin cycle repeats in the same way everyday, mammals' bodies are sensitive to seasonal changes in the length of the day, so the cycle's timing changes with the season. The retinohypothalamic tract, the network connecting the light-sensitive retina in the eye to the hypothalamus in the brain, registers light input and changes the timing of the circadian pacemaker. As a consequence, the duration of increased neuron firing (the "alarm clock ringing") lengthens as the days lengthen in spring and summer, and shortens as days grow shorter in fall and winter. This creates different seasonal patterns in melatonin secretion and therefore in mammalian behavior and mood.

Wondering whether the circadian pacemaker might also explain seasonal patterns in humans (and thus relate to Seasonal Affective Disorder), Thomas Wehr, Wallace Duncan, Leo Sher, and Daniel Aeschbach studied variations in the length of the period of nocturnal melatonin secretion. Their 2001 study showed that this nocturnal period (when the "alarm clock" is off and melatonin production is high) was 38 minutes longer in winter than in summer in patients with SAD. Unaffected people, however, showed no seasonal variation in duration of nocturnal melatonin secretion (4). While it seems that 38 minutes would be a relatively small difference, especially given the greater seasonal changes in day length, studies in other mammals have shown significant behavioral effects from such short shifts; reproductive functions in hamsters, for example, were significantly impacted by variation in day lengths of as little as thirty minutes (4). The Wehr et al. study shows that, like mammals, humans with SAD bioregulate according to the seasons in a way that humans without SAD do not. These results lend support to the "melatonin hypothesis," which attributes SAD to "abnormal secretion of or sensitivity to melatonin" (2).

Abnormal release of serotonin, a neurotransmitter that helps regulate mood, is another potential "culprit." Poor transmission of serotonin and the neurotransmitter neuropeptide Y, which regulates appetite, to the circadian pacemaker may help explain some of the mood and appetite disturbances that are symptomatic of SAD. In fact, melatonin can affect these two neurotransmitters, demonstrating two potential effects of the irregular melatonin cycling described above (1). Other studies have also found that SAD symptoms such as overeating (especially carbohydrates) and oversleeping can be related to abnormalities in the serotonin system (2). Understanding that the probable mechanism of SAD is abnormal functioning of the circadian pacemaker and related biochemical systems immediately suggests possible avenues of treatment directed at "resetting the biological clock."

SAD in Genes and Families
Genetic differences underlie the chemi-

cal differences between SAD patients and unaffected people. For example, one component of the serotonin transport system, whose importance was described above, is coded for by a gene Rosenthal and his colleagues studied in 1998. A given gene can have multiple variations, or allele polymorphisms, and every human has two versions of most of their genes. The gene coding for the serotonin transporter (labeled 5-HTTLPR) comes in two forms labeled "long" and "short." So, a given person's genetic profile, or genotype, could have two long alleles, two short alleles, or one long and one short. Rosenthal found that genotypes with at least one short allele were found more often in SAD patients than in unaffected people. Interestingly, this form of the gene had been previously associated with other disorders including major depressive disorder. Additionally, SAD patients who had two long alleles (the typically "non-SAD" genotype) had milder SAD symptoms than SAD patients with at least one

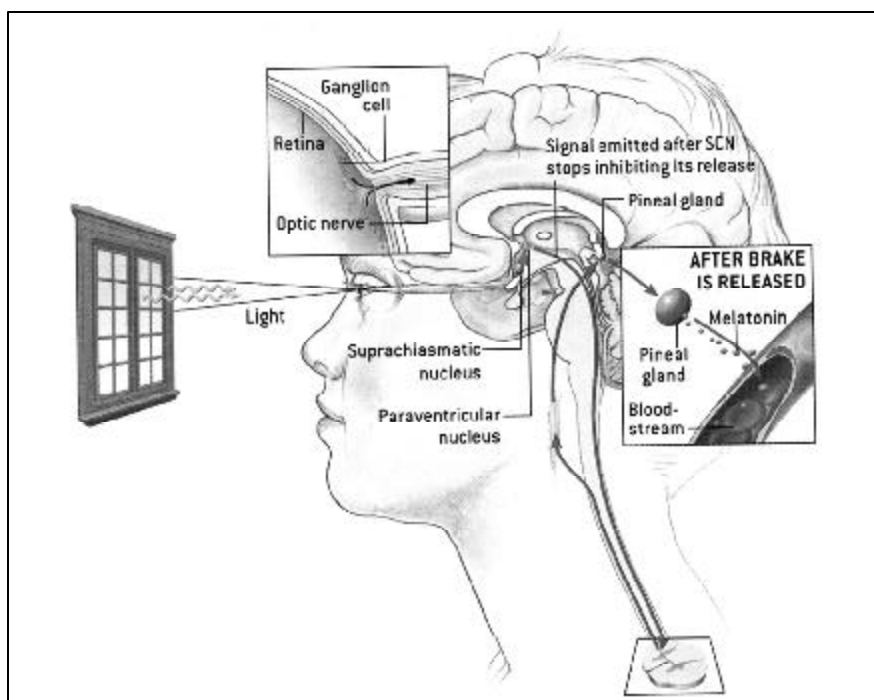


Figure 1. Light travels from the retina in the eye to the circadian pacemaker (SCN) in the hypothalamus, where it causes the pineal gland to decrease production of melatonin as the body awakens. After dark, the SCN releases the brake, allowing melatonin to be secreted. This hormone and the neurotransmitter serotonin regulate the body's adjustments to sleeping and waking cycles. Problems in these pathways are the likely mechanisms producing SAD symptoms.

credit: Terese Winslow. "Times of our lives." Scientific American. September 2002.

short allele (the typically “SAD” genotype) (1). These results bolster the theory that SAD and seasonality are caused by an abnormal serotonergic system.

If SAD has a genetic basis, genes predisposing someone to SAD could be inherited. Several studies on families of SAD patients have observed this hereditary pattern, finding that “between 13 and 17% of first-degree relatives [of SAD patients] appeared to be affected by SAD and between 25 and 67% of the relatives had non-seasonal mood disorders” (1). “This compares to population prevalences between 1.4 and 9.7% for SAD (Rosen et al., 1990), and between 8 and 20% for non-seasonal mood disorders (Blazer 1995)” (2). In other words, there is a much higher risk of SAD for close family members of a SAD patient than there is for members of the general population: about ten percent more, doubling or even tripling the risk. It is also significantly more likely that family members of SAD patients will suffer from other, non-seasonal mood disorders, a several-fold increase in risk. While some of the methodology of these studies has been called into question, the results nevertheless begin to address the question of whether SAD runs in families. A similar study using different methodology found that in families of SAD patients, a remarkable 65% of members had some kind of psychiatric disorder, suggesting that SAD does have some genetic and familial relationship to other disorders. This suggestion has been further supported in studies of identical and fraternal twins, which showed that genetics significantly helped explain the appearance of winter seasonality and that “seasonality tends to run in families” (2).

Sunshine in a Box

Scientists now believe that the most likely cause of SAD at the level of chemical regulatory mechanisms is ab-

normal functioning of the circadian pacemaker system, possibly keyed to insufficient or irregular exposure to natural light, as discussed above. A logical treatment, then, would be to use light to “reset” the body’s circadian rhythms and reduce the symptoms of SAD. As it turns out, the Greeks came to a similar conclusion centuries ago. As early as the second century AD, “Greco-Roman physicians were treating depression and lethargy with sunlight directed towards the eyes” (2).

Not surprisingly, light therapy has emerged in modern medicine as well as the main treatment for winter SAD. In the home, visible light is typically produced at or less than 100 lux (a measure of illumination per square meter); on the job, light levels are between 300 and 500 lux. In comparison, however, ambient light levels outdoors range from 2000 lux on a rainy winter day to more than 10,000 lux in bright sunlight. It is easy to see how relatively little light exposure one can actually receive during the day from indoor light sources, so scientists have developed and refined a “bright-light treatment” that effectively brings the outdoors inside. During a typical bright-light treatment, the patient is exposed to two hours of 2,500 lux light from a home “lightbox” for a period of two hours; this may need to be continued daily, or at least five days a week, throughout the winter. It is now generally believed that the best time for this exposure is early morning, as a kind of simulated dawn (1). Morning bright-light therapy may effectively kick-start the circadian pacemaker neurons to generate the “wake up” signal that also curbs symptoms

like lethargy and depression. The relative success of this treatment, which improved 67% of mild cases and 40% of moderate to severe cases in one study (1), supports the hypothesis that SAD is based upon irregular circadian rhythm regulation.

Another promising treatment for winter SAD also addresses the brain’s neurochemical regulatory systems, but internally rather than externally. In particular, interfering along the path from gene expression to serotonin production, release, and reabsorption effectively treats SAD. For example, a specific type of antidepressant known as an SSRI, a selective serotonin-reuptake inhibitor, prevents the reuptake of serotonin, leaving more in the system and therefore making up for low levels of production or release earlier in the pathway. Treatment with SSRIs like



Figure 2. Bright light directed to the eyes has been shown to reduce symptoms of seasonal affective disorder. Though not yet scientifically proven alternatives to light boxes (top), light visors (left) make bright light therapy more convenient. Because abnormal fluctuations of melatonin, a brain chemical that regulates sleep cycles and related mood and behavior changes, may help explain seasonal affective disorder, melatonin supplements (right) are also a possible treatment being investigated.

credit: <http://www.ask4mass.com/images/kaizen/melatonin.jpg> <https://www.sunbox.com/Products/OtherProducts.asp>

sertraline and fluoxetine (Prozac) have shown “promising results” in clinical trials (1).

Diagnosis

The most commonly used diagnostic tool for SAD is the Seasonal Pattern Assessment Questionnaire developed by Norman Rosenthal, on which the subject rates the seasonal variation in his sleep, social, mood, weight, appetite, and energy-level patterns. The subject is also asked to report the month when they feel “worst” and the degree to which they feel seasonal changes are a problem. The reliability of this test has been called into question in some applications because of variability in results depending on the season and weather conditions when it is administered, as well as inconsistent responses that may be due to misunderstanding the directions (7). Still, it remains the most effective and well-established tool for diagnosing SAD.

However, we clearly know more about SAD than just its symptoms, so more factors can and should be considered when evaluating the likelihood of SAD or making a diagnosis. For instance, SAD researchers Leo Sher, David Goldman, Norio Ozaki, and Norman Rosenthal write, “the fact that there is a genetic predisposition to SAD” and a greater prevalence in individuals and families with evidence of seasonality and seasonal affective and other non-SAD disorders “shows the importance of a thorough diagnostic interview [including] questions on the family history of SAD, seasonality, and other behavioral disorders” (2). Current knowledge on the role of genetics in SAD points to the need for more comprehensive diagnostic criteria than the results of the Seasonal Pattern Assessment Questionnaire, which only addresses an individual’s history of symptoms.

An extremely valuable next step in SAD research would therefore be the development of a predictive genetic

test based upon genetic variations that are more prevalent in people susceptible to SAD. While we are very far from creating any kind of genetically based treatment for SAD, Sher and associates believe that an understanding of the genetics of SAD will permit a better understanding of the effects of its environmental factors as well. This is not a case of nature versus nurture. Though SAD likely has its roots at the genetic level, it has its expression at the level of psychology and behavior. Treatment at this physiological or environmental level (such as light therapy or therapeutic drugs) “may diminish or override the effect of genetic risk factors for SAD” (2). Even if we cannot change the presence of a SAD genotype (a genetic profile with a greater risk of SAD), we can treat and change the SAD phenotype at the symptomatic level and its harmful effects on the lives of those suffering from SAD.

Bright Futures

Since Rosenthal and associates formally defined Seasonal Affective Disorder in 1984, scientists’ and physicians’ insight into the causes, diagnosis, and treatment of SAD has increased dramatically. Continued examination of the serotonin and melatonin systems and the actions of the circadian pacemaker will help us better understand both why SAD symptoms occur and how we can best treat them. At the genetic level, the development of a way to evaluate genetic risk factors for SAD and a predictive genetic test to be used in conjunction with individual and family history questionnaires would give physicians powerful tools to make conclusive and early diagnoses of SAD.

Another fascinating lines of inquiry remains: What can we learn from SAD about the relationship between modern human life and the natural environment? Why do people with

SAD experience seasonal changes like other mammals do, but healthy humans do not? With or without SAD, we no longer experience regular cycling of day and night as we used to – alarm clocks wake us up before dawn, we stay indoors out of the sun all day, and artificial light extends the “day” late into the night. So, more work remains in the examination of how humans in their everyday environments experience and respond to signals of light, day length, climate, and season, and how these signals interact with genetic and chemical factors to produce the symptoms of SAD. We are already well on our way to understanding this disorder and continued advances in diagnosis and treatment will allow us to offer SAD sufferers an ever brighter future.

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