Potential animal models of seasonal affective disorder

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ABSTRACT

Seasonal affective disorder (SAD) is characterized by depressive episodes during winter that are alleviated during summer and by morning bright light treatment. Currently, there is no animal model of SAD. However, it may be possible to use rodents that respond to day length (photoperiod) to understand how photoperiod can shape the brain and behavior in humans. As nights lengthen in the autumn, the duration of the nightly elevation of melatonin increase; seasonally breeding animals use this information to orchestrate seasonal changes in physiology and behavior. SAD may originate from the extended duration of nightly melatonin secretion during fall and winter. These similarities between humans and rodents in melatonin secretion allows for comparisons with rodents that express more depressive-like responses when exposed to short day lengths. For instance, Siberian hamsters, fat sand rats, Nile grass rats, and Wistar rats display a depressive-like phenotype when exposed to short days. Current research in depression and animal models of depression suggests that hippocampal plasticity may underlie the symptoms of depression and depressive-like behaviors, respectively. It is also possible that day length induces structural changes in human brains. Many seasonally breeding rodents undergo changes in whole brain and hippocampal volume in short days. Based on strict validity criteria, there is no animal model of SAD, but rodents that respond to reduced day lengths may be useful to approximate the neurobiological phenomena that occur in people with SAD, leading to greater understanding of the etiology of the disorder as well as novel therapeutic interventions.

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Seasonal affective disorder was first described in 1984 (Rosenthal et al., 1984) and exists in the Diagnostic and Statistical Manual not as an independent diagnosis, but as a specifier of either unipolar or bipolar affective disorders (American Psychiatric Association, 2000). Seasonal variations in both temperature and photoperiod appear to precipitate two forms of SAD; the summer form (Wehr et al., 1991; Wehr et al., 1987), and the winter form (Rosenthal et al., 1984). Human research has primarily focused on the winter form of SAD which seems to manifest from a reduction in day length. The summer form of SAD, which is the seasonal inverse of the winter form, may result from high temperatures (Wehr et al., 1987) or may also manifest from high allergen load which in turn may lead to depressive symptoms by activation of inflammatory pathways (Guzman et al., 2007). This review will focus on the winter form of SAD. The winter-type SAD manifests as atypical symptoms of depression that recur in the fall and winter, such as depressed mood, anhedonia, decreased activity, decreased libido, hyperphagia, hypsomnia, carbohydrate craving, fatigue, and weight gain (Jacobsen et al., 1987; Rosenthal et al., 1984). These symptoms remit in the spring or summer and individuals can become either euthymic or hypomanic (Rosenthal et al., 1984). Symptoms also remit in response to morning exposure to bright light greater than 2500 lux (Eastman et al., 1998; Ruhrmann et al., 1998). As is the case with other affective and anxiety disorders, significantly more women than men are diagnosed with SAD. This sex difference is especially present during the reproductive years and may be hormonally based (Kasper et al., 1989).

Although SAD is a seasonally recurring disorder, evidence suggests a circadian basis for winter-time depression (Lewy et al., 2006; Wehr et al., 2001). The phase shift hypothesis (PSH) proposes that SAD sufferers experience a circadian phase delay in the winter and that bright light in the morning reduces symptoms by inducing a phase advance in circadian rhythms (Lewy, 1999; Lewy et al., 2006; Lewy et al., 1987), although a significant majority of SAD suffers may also experience a phase advance. Melatonin, the physiological signal of darkness, can be assayed through saliva and used as a phase marker (Lewy, 1999). Dim light melatonin onset (DLMO) in the evening can be assayed to determine if individuals are phase advanced, and melatonin secretion may be a form of self medication as carbohydrates increase plasma tryptophan, the precursor for serotonin (Möller, 1992). Additionally, catecholamine depletion also caused remission after light therapy (Neumeister et al., 1998b). Selective serotonin reuptake inhibitors also reduce symptoms of SAD, which further implicates monoamines in this disorder (Ruhmann et al., 1998). Interestingly, however, some antidepressants (SSRIs, to be specific) may also exert therapeutic effects by inducing a phase advance, thus correcting the phase delay present in SAD (Murray et al., 2005).

Currently, there is no suitable animal model of SAD, but understanding the neurobiological phenomena that underlie affective responses to changes in day length is paramount in understanding SAD in humans. The intent of this review is to discuss current knowledge surrounding affective responses to changes in day length in both photoperiod-responsive and nonresponsive rodents. Although we contend that no species fully models all symptoms of SAD, some species may be used to model different components of SAD. We propose that some species that undergo behavioral changes in response to short day lengths may especially be useful in studying pathophysiological responses to short days. Indeed, traditional model species (mice and rats) are likely inappropriate to model SAD because responsiveness to day length has been artificially selected against in the laboratory. Thus, outbred species are preferable as models of SAD. In this review we will briefly explore the evolutionarily benefits of seasonal changes in depression-associated behaviors and finally, some alternative explanations of SAD independent of photoperiodism and melatonin.

1.1. Seasonal affective disorder: clinical phenomena and physiological correlates

Climates on earth are characterized by fluctuations in temperature, precipitation, and humidity, which lead to differential distribution of resources across a year. In many temperate regions, winters are characterized by low temperatures and food is much less abundant than during summer. The ability to predict such seasonal variation and coordinate energetically expensive processes (such as breeding) with mild ambient conditions greatly enhances the probability of survival of not only individuals, but also of their offspring. Whereas many tropical regions also undergo seasonal fluctuations in food availability due to variations in rainfall, this review will focus on seasonality as it applies to nontropical regions. Specifically, organisms have evolved to time endogenous processes to coincide with specific external conditions. They accomplish this goal by physiologically assessing day length (photoperiod), a process called photoperiodism (Nelson et al., 2010). In nontropical regions, there is enormous variability in weather conditions (such
as temperature) within a season, which precludes these factors as signals for biological rhythms that occur on a seasonal basis. On the contrary, day length follows a predictable annual sinusoidal pattern and as such, many organisms use this cue as a signal to either cease reproduction, as many seasonally breeding rodents do when day lengths wane, or to stimulate reproduction, as many seasonally breeding birds do when day lengths wax.

Seasonal rhythms can either be fully endogenous (also termed a type II rhythm) or endogenous/exogenous (type I rhythm) (Prendergast et al., 2002, 2009). That is, fully endogenous rhythms persist in the absence of an exogenous signal for at least two cycles. For example, seasonal body mass rhythms in golden-mantled ground squirrels (Spermophilus lateralis) continue to fluctuate in a constant light–dark cycle in the laboratory (Lee et al., 1986). Type I rhythms, on the other hand, rely (at least partially) on the presence of an exogenous signal. For example, among Siberian hamsters (Phodopus sungorus) reproductive processes are inhibited by the presence of shortening day lengths and will spontaneously re-emerge when hamsters become refractory to short day lengths (Hoffmann, 1978; Kaufman et al., 2003). Because seasonally breeding rodents respond robustly to day length, seasonal changes can be modeled in the laboratory by adjusting light exposure. Changes in reproductive behavior and physiology in seasonally breeding rodents have been well characterized both in the laboratory setting and in the field, but other behaviors also vary as a function of day length. In common with reproductive processes that occur when photoperiod predicts optimal seasons, seasonal variation in nonreproductive behaviors may also be adaptive.

For instance, many small seasonally breeding rodents display changes in learning and memory that occur as a function of day length (Peramyscus polionotus; Trainor et al., 2007a, 2007b) increase aggressive behaviors in short days. Heightened aggression in short days is likely adaptive for securing resources during harsh winters (Demas et al., 2004), a function of winter-aggression that has been documented among migratory and resident birds (Schwabl, 1992; Tinbergen, 1957). Siberian hamsters also undergo changes in affective responses dependent on day length. Specifically, short days increase depressive-like behavioral responses as measured in the forced swim test (Prendergast and Nelson, 2005; Pyter and Nelson, 2006), a behavioral test designed in the 1970s to screen antidepressant drugs (Porsolt et al., 1977). Short days also increase anxiety-like behaviors in some behavioral tests (Prendergast and Nelson, 2005; Pyter and Nelson, 2006). The adaptive significance of these behavioral changes is less clear than the aforementioned behaviors: however, some investigators have proposed interesting hypotheses regarding how the proclivity for depressive-like behaviors or depressed mood may increase the likelihood of survival in particular circumstances.

1.2.1. Seasonality in humans

Although humans appear to lack significant reproductive responsiveness to changes in season or day length, population evidence suggests that there are subtle annual variations in conception and birth rate (Bronson, 2004; Lam and Miron, 1991; Roenneberg and Aschoff, 1990a,b). Many sociocultural factors may be at play in establishing these seasonal rhythms, but day length nevertheless may be an important cue in inducing a peak of conceptions during the spring equinox (Roenneberg and Aschoff, 1990b; Foster and Roenneberg, 2008). Further, Bronson (2004) suggested that perhaps only a proportion of humans are responsive to day length, which may explain why other investigators found no relationship between day length and conception rates (Lam and Miron, 1991) and why not all people experience SAD upon exposure to short days. In addition to reproduction, a number of other phenomena vary seasonally, including mortality rates, cardiac arrest, rape, violent crimes, and suicide. Psychological variables also fluctuate seasonally. For instance, bulimia nervosa (Blouin et al., 1992), sleep (Kohsaka et al., 1992), rates of suicide (Partonen et al., 2004), and the peak of the inpatient population (Tentte, 1989) all vary seasonally. Although it is as yet unclear whether photoperiodic changes drive these seasonal phenomena, evidence strongly suggests that winter day lengths are what control the winter form of SAD.

SAD is certainly the most well known of psychiatric phenomena occurring with a seasonal pattern and has gained increasing attention after its first description (Rosenthal et al., 1984) and after the discovery that bright light treatment could inhibit melatonin secretion in humans (Lewy et al., 1980) and alleviate symptoms (Rosenthal et al., 1985; Wehr et al., 1986). Research in seasonal affective disorder also underscores Bronson’s hypothesis, given that not all individuals are at risk for seasonal variations in mood. However, some research suggests that a proportion of individuals undergo subclinical fluctuations in affect, termed subsyndromal SAD (S-SAD; Austen and Wilson, 2001; Kasper et al., 1989). Because humans have the anatomical pathways associated with converting day length into a physiological signal (Wehr et al., 2001), it is possible that changes in photoperiod are responsible for altering mood and behavior in a seasonal pattern in at-risk individuals.

1.2.2. Putative adaptive function of seasonal depression

The field of evolutionary medicine has yielded fascinating insights regarding the ultimate explanations for depressed mood and learned helplessness. This is certainly not to say that major depression itself has evolutionary benefit. Although depression is a debilitating disorder that is painful and maladaptive for affected individuals and their friends and families, it is possible that the propensity to experience low mood and reduced motivation may have been selected as an adaptive mechanism in particular contexts (Keding and Nesse, 2005; Nesse, 2000). A comparison with fever may help clarify this apparent paradox: fever, when maintained below a particular temperature, is adaptive for the host as it may help eradicate a viral, bacterial, or parasitic infection (Kluger, 1978; Nesse and Williams, 1994). However, the processes controlling febrile responses may become dysregulated; fever can become too high which places organisms at risk for brain damage. Affective responses that are adaptive in some contexts may also become dysregulated. An understanding of the evolutionary benefit of depressed mood becomes especially salient when considered in seasonal context. Seasonal depression may represent a vestigial advantage in terms of survival and reproduction (Eagles, 2004). The behavioral consequences of low mood, such as disengagement from a task (foraging, for example) may have evolved as a means of conserving energy reserves (Nesse, 2000) which may have been especially important in winter when energetic demands are high and food availability is low. Behavioral inactivity may save considerable energy in winter. In fact, Eagles (2004) contends that SAD may represent a vestigial form of hibernation due to the similarities between autonomic control in SAD sufferers and in hibernating mammals. In individuals with SAD, parasympathetic control is enhanced (Austen and Wilson, 2001) and in hibernating
ground squirrels parasympathetic control over the heart increases during the initiation of hibernation, but then is reduced while hibernation is maintained (Milsom et al., 1999). Perhaps a more apt comparison is between autonomic control in SAD sufferers and that of other nonhibernating seasonally breeding mammals. In Siberian hamsters, short days increase resting vагal tone (Weil et al., 2009) in common with SAD sufferers. Eagles (2004) also argues that winter depression would have increased the likelihood of spring and summer births. Low mood, and consequently social withdrawal during the winter, may have evolved to prevent energetically expensive processes, such as reproduction, from occurring in the winter. Finally, low mood in the winter may have been a means of manipulating others in a social group into providing resources. The possibility that SAD represents vestigial adaptations to a seasonally changing environment underscores the importance of cross-species comparisons with mammals that evolved behavioral and physiological changes that coincide with changes in day length. Additionally, if SAD does arise from vestigial adaptations, then validity of an animal model may be more readily achieved because it suggests there may be homologous processes that regulate seasonal changes in affect in humans and photoperiod-related affective responses.

2. Animal models

2.1. Current animal models of nonseasonal depression

Current animal models of depression employ a number of techniques to induce and assess depressive-like phenotypes. Chronic stress (Willner, 1997, 2005; Willner et al., 1992), social defeat, disruption (Becker et al., 2008) or isolation (Wallace et al., 2009), olfactory bulbectomy (Song and Leonard, 2005), chronic corticosterone administration (Murray et al., 2008), and genetic manipulations can all induce depressive-like behaviors which are typically assessed by the forced swim test, tail suspension test, or sucrose anhedonia test (Willner, 1997; Willner et al., 1992). Many of these models rest on the assumption that chronic stress (increases in cortisol or corticosterone) or dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis precipitates depressive episodes. There is an intimate relationship between cortisol and depression. Depressed individuals display disruptions in HPA axis function (Young et al., 2000). Hippocampal atrophy is another common feature of animal models of depression, and depression in humans (Sheline et al., 1996), and seems to be a consequence of dysregulated cortisol secretion (corticosterone in mice and rats; McEwen, 1999, 2001). Additional evidence supporting this relationship is that in Cushing’s disease, the adrenal glands produce excessive amounts of cortisol which is associated with hippocampal atrophy, cognitive dysfunction (Starkman et al., 1992), and depression (Condren and Thakore, 2001). Chronic stressors in male rodents induce dendritic retraction in the CA3 region of the hippocampus (Watanabe et al., 1992) and reduce hippocampal neurogenesis (Gould and Tanapat, 1999). These changes are reversible, however, as administration of antidepressants (such as tricyclics and selective serotonin reuptake inhibitors) restore neurogenesis (Malberg et al., 2000; Santarelli et al., 2003) and the integrity of hippocampal dendrites (Bessa et al., 2009; Wang et al., 2008). Prefrontal cortical remodeling also occurs after chronic stressors in models of depression and can be reversed by antidepressant treatment (Bessa et al., 2009). Environmental factors, such as access to a running wheel and social housing also restore or protect hippocampal processes and reduce negative affective and stress responses (Benaroja-Milshtein et al., 2004; Diamond, 2001; van Praag et al., 2000). However, significant deviations in HPA axis hormones do not occur in people with SAD compared with healthy individuals (James et al., 1986; Oren et al., 1996).

Could hippocampal structure and function be compromised during the winter in SAD sufferers? Certainly, there is overwhelming evidence to link hippocampal atrophy to major depressive disorder, but to our knowledge, no studies have reported hippocampal volumes from imaging data in participants with SAD. Pituitary volume, however, has been investigated, but it does not vary on a seasonal basis or after phototherapy in individuals with SAD (Miranda-Scippa et al., 2008). Additionally, a study using positron emission tomography has shown global reductions in metabolic processes in the brains of people with SAD (Cohen et al., 1992). Interestingly, SAD is also associated with cognitive deficits: some studies have conducted hippocampal- and prefrontal cortical-dependent cognitive tasks with individuals diagnosed with SAD and report that scores on the Cognitive Failures Questionnaire are compromised in people with either MDD or SAD (Sullivan and Payne, 2007). In people with SAD, deficits were reported in both working and spatial memory (O’Brien et al., 1993), which implicates the prefrontal cortex and hippocampus, and deficits occur in both men and women with the disorder. Along with affective and somatic symptoms, most cognitive deficits of SAD sufferers remit during summer and light treatment (O’Brien et al., 1993). This suggests that hippocampal and prefrontal cortical plasticity may be compromised in the winter in SAD sufferers and, if so, these processes are likely to underlie depressive winter symptoms. There is overwhelming evidence from small mammals and birds that short day lengths induce structural changes in the brain and this observation has adaptive functional implications.

2.2. Potential models of SAD

An evaluation of the utility of animal models of SAD in the late 1980s led to the conclusion that, strictly speaking, there are no viable animal models of SAD (Zucker, 1988). We contend that this is still the case based on strict validity guidelines. However, we also contend that (as in the aforementioned review) photoperiod-responsive animals offer great utility in investigating seasonal variations in both pathological and nonpathological processes in humans. We will address the similarities between photoperiodic and nonphotoperiodic rodents exposed to short days and the symptomatology of SAD. Nonphotoperiodic rodents are those that do not use day length to time seasonal breeding cycles. However, they may still retain the capacity to respond to day length in other regards. First, a brief discussion of the validity of animal models of depression is warranted.

In order for an animal model to be considered valid, there are three criteria that must be met. First, the model must have face validity and provide a reasonable outward representation of the disorder (i.e., the behavioral phenotype matches the symptoms of the disorder). For example, Siberian hamsters have some face validity because they increase floating in the forced swim test, and have an extended duration of melatonin secretion, just as occurs in SAD, but do not display anhedonia or increased body mass in short days. Second, a model has predictive validity if the effect of pharmacological agents is the same in the model as it is in the human population of interest. For example, fluoxetine should reduce symptoms. Finally, a model has construct validity if the model behaving the same underlying mechanisms, or etiology and is homologous to the human disorder (Willner, 1984). Both changes in SAD and changes in behavior in Siberian hamsters are caused by changes day length.

Previously, we have established that short days induce a depressive-like phenotype in the forced swim test (Prendergast and Nelson, 2005; Workman and Nelson, unpublished observations; Pyter and Nelson, 2006). Also, in collared lemmings...
Short and intermediate photoperiods increase anxiety-like responses. However, photoperiod-induced changes in depressive-like responses in this study were less obvious, but a sex difference in responses was apparent; females displayed more behavioral despair, which mirrors the clinical pattern in affective disorders (Weil et al., 2007). Female meadow voles (Microtus pennsylvanicus) also display more anxiety-like responses than males, but exposure to long photoperiods was anxiogenic, which may derive from seasonal differences in predation risk (Ossenkopp et al., 2005). Numerous other studies indicate that rodents that do not respond reproductively to day length display a number of traits that are modulated by photoperiod, including negative affective responses (Ashkenazy et al., 2009b; Molina-Hernandez and Tellez-Alcantara, 2000; Prendergast and Kay, 2008). Additionally, house mice typically do not respond reproductively to photoperiod will respond under certain circumstances, which suggests that they have maintained responsiveness to photoperiod while other processes have masked reproductive responsiveness to short days (Nelson, 1990). Clearly, humans also do not display significant reproductive responsiveness to day length, though mood of some individuals is affected by day length. Thus, which species will best model SAD?

Certainly, no animal model will comprise all symptoms of a given disorder. Indeed, not even all humans exhibit all symptoms when diagnosed with a particular disorder or disease. However, different model species may be useful in modeling specific aspects of SAD. For example, Siberian hamsters do not seem to alter sucrose consumption upon exposure to short days (Pyter and Nelson, 2006; Workman and Nelson, unpublished observations); thus, they do not optimally model anhedonia present in some individuals with SAD. However, nonreproductively photoperiodic Wistar rats (Prendergast and Kay, 2008) and fat sand rats (Psammomys obesus) (Ashkenazy et al., 2009b) do reduce sucrose consumption when exposed short days. Many animal models are also limited in their comparison to humans because most models have been nocturnal rodents. However, several recent studies have investigated diurnal rodents and report similar short-day affective responses (Ashkenazy-Frolinger et al., 2010; Ashkenazy et al., 2009a,b). However, these studies use comparatively extreme light–dark cycles (5:19 LD), whereas many people develop SAD at latitudes with only moderately short day lengths in the winter. Thus, a multi-pronged approach using both inbred and outbred rodents, reproductively responsive and nonresponsive rodents, and diurnal and nocturnal rodents should prove useful for investigating how photoperiod influences affective processes. It should also be noted that one major limitation of many of the aforementioned studies is that they demonstrate a male sex bias, which is especially regrettable for studies in modeling affective and anxiety disorders because women are at a greater risk for affective dysregulation, including SAD. It is assumed that the estrous cycle induces greater variability in behavior (Palanza, 2001), but this assumption can be challenged (Beery and Zucker, 2010). Previous studies in our lab have investigated affective responses in female Siberian hamsters with mixed results (see Table 1 for summary). It may not be appropriate to compare short-day anestrous females to long-day, cycling females because estrogens affect activity levels as well as anxiety- and depressive-like responses (Walf and Frye, 2006, 2007). Therefore, it will be necessary to investigate how short days influence affective responses in nonreproductively photoperiodic females. The aforementioned species also do not exhibit increased caloric intake or carbohydrate craving consistent with the symptoms of SAD. Siberian hamsters display a metabolic strategy in which they lose weight when exposed to short days, which in turn reduces energetic demands and food intake (Bartness and Wade, 1985; Wade and Bartness, 1984a). In contrast, Syrian hamsters (Mesocricetus auratus) are reproductively photoperiodic and display increases in body mass in short days (Bartness and Wade, 1985; Wade and Bartness, 1984b), but have not been tested in affective behavioral measures. In male Sprague-Dawley rats fed a high fat diet, short photoperiod exposure increased consumption of a sucrose solution and body mass over the course of the study (Sinitskaya et al., 2008) which may model the carbohydrate craving evident in SAD. This may seem contrary to the reduction in hedonic drive expected in models of depression, however this sucrose consumption test is methodologically different from the one used to assess anhedonia. In the previous study, a 10% sucrose solution was used to monitor caloric consumption whereas in studies of anhedonia, a 1–3% solution is used. The sucrose anhedonia test is designed to be independent of caloric needs and dependent upon the rewarding properties of the stimulus (and thus, nucleus accumbens processes; Willner et al., 1992). This is an important distinction because many of the aforementioned species undergo changes in metabolic processes coincident with changes in day length and hedonic processes should be somewhat distinct from motivation to consume food. Finally, the above comparisons are only valid if the traits serve a similar adaptive function in humans (Zucker, 1988).

2.3. Seasonal and photoperiodic changes in brain and hippocampus

The best documented account of seasonal brain plasticity comes from research with birds. As birds become refractory to long day lengths, the song control nuclei in their brains undergo dramatic volume reductions and singing behavior is virtually absent.
as previously mentioned, increase negative affective responses in short days and thus may be used to investigate hippocampal changes that underlie photoperiod-associated changes in affective responses. Preliminary data from our lab indicate that Siberian hamsters undergo a retraction of CA1 dendrites, a reduction in cell body size in the CA1 region, and increased spine density in the dentate gyrus after exposure to short days, which may be related to short-day-induced increases in depressive-like behavior (Workman and Nelson, unpublished observations). The behavioral significance of changes in the CA1 versus CA3 region remains unspecified, although changes in both regions have been correlated with spatial learning and memory (Sorra and Harris, 2000; Workman et al., 2009). Although traditionally considered a structure underlying learning and memory, the role of the hippocampus in emotional behavior is becoming increasingly apparent. However, a dissociation of the individual roles of the CA1 and CA3 regions in emotional responses remains to be described. Studies investigating how short day lengths modulate cell morphology in the prefrontal cortex are also currently underway in our laboratory.

2.4. Putative neuroendocrine and immune mechanisms of seasonal depression and brain plasticity

The list of hormones that act on brain plasticity and affective responses is extensive (Galea, 2008; Gould et al., 1991). If, however, a particular species is selected as a model for SAD, then photoperiod-induced changes in affective responses should be, by-and-large, independent of fluctuations in gonadal hormones because of the lack of change in gonadal hormones in humans across a year. In Siberian hamsters, many seasonally fluctuating nonreproductive traits are independent of circulating gonad hormones. For example, short-day increases in aggression are independent of gonadal hormones; rather, these behavioral adjustments are mediated by melatonin and adrenal hormones (Demas et al., 2004). Although testosterone may facilitate spatial learning and memory in many circumstances, castration does not impair spatial learning in long-day white-footed mice (Pyter et al., 2006). Additionally, castration also does not prevent short-day enhancement of cell-mediated immune function in Siberian hamsters (Prendergast et al., 2005). Thus, many processes fluctuate as a function of day length but are, at least partially, independent of gonadal hormones. It is possible that melatonin directly,
or indirectly via downstream hormones, mediates these changes, as well as affective changes, but depressive-like responses have not yet been investigated in seasonally breeding gonadotropinized rodents.

As mentioned, hypothalamic-pituitary-adrenal (HPA) axis hormones are dysregulated in major depression and changes in hippocampal, prefrontal, and amygdalar plasticity are induced by chronic stressors (McEwen, 2005). Similar disruptions in HPA axis function do not seem to manifest in people with SAD. For example, the dexamethasone suppression test in people with SAD yields the same concentrations of cortisol in people without a depressive disorder suggesting that negative feedback processes are not disrupted (James et al., 1986). Nor do circadian profiles of cortisol secretion differ between people with and without SAD (Oren et al., 1996). Thyrotropin-secreting hormone (TSH) profiles also do not differ between people with and without SAD (Oren et al., 1996).

Therefore, changes in affective responses and brain plasticity in animals could be largely independent of these endocrine systems as well.

Conflicting results exist regarding the effect of melatonin on brain plasticity and behavior. From an ecological perspective, duration of melatonin secretion is responsible for orchestrating yearly fluctuations in physiology and behavior. Short-days lengthen the duration of nightly melatonin secretion in Siberian hamsters which presumably influences depressive-like responses. Melatonin is not always assessed directly, but photoperiod-responsiveness is confirmed through tests mass at necropsy or estimated testis volume in anesthetized animals. Melatonin administration in a physiological pattern mimicked the responses induced by exposure to short days in fat sand rats (Ashkenazy et al., 2009b). From a pharmacological perspective, however, melatonin administration appears to reduce depressive- (Ramirez-Rodriguez et al., 2009) and anxiety-like responses (Kopp et al., 1999). Supraphysiological doses of melatonin also increased cell survival in the dentate gyrus of the hippocampus (Ramirez-Rodriguez et al., 2009). These latter results suggest that melatonin in high, acute doses may facilitate hippocampal plasticity perhaps by acting as a free-radical scavenger (Poeppele et al., 1994). It is important to consider the physiological pattern of melatonin secretion and studies aiming to model SAD should mimic a short-day extension of melatonin, rather than pro-estrogens that manipulate prolactin signaling through either administering prolactin in medium or people diagnosed with SAD are lower than those without SAD (Oren et al., 1996; but see also Danilenko and Putilov, 1993). Similarly, short-days also reduce prolactin concentrations in Siberian hamsters which facilitates molt to a white pelage (Duncan and Goldman, 1984) and torpor (Ruby et al., 1993), both of which are presumed adaptive winter processes. Indeed, regardless of whether individuals breed under long or short day lengths, all species reduce prolactin concentrations in response to short days (Nelson, 1999). Prolactin supplementation protects the hippocampus from stress-induced decrements in neurogenesis (Tonner et al., 2009), but the functional importance of this protection is unknown. The hippocampus contains prolactin receptors which makes it possible for prolactin to modulate neuroplastic processes directly and in turn modulate affective responses. Studies that manipulate prolactin signaling through either administering prolactin or a receptor antagonist in photoperiodic rodents would be informative.

Lastly, inflammatory processes could mediate seasonal changes in mood in people with SAD (Lam et al., 2004). In people with major depression, inflammatory processes are disrupted and immune manipulations (such as treatment with cytokines) can precipitate depressive episodes (for review, see Raison et al., 2006). Photoperiod-induced changes in immune processes in seasonally breeding rodents are well documented (for review see Nelson, 2004). In Siberian hamsters, short days enhance antigen-specific immune processes (Bilbo and Nelson, 2003; Prendergast et al., 2005). Melatonin can mediate immune processes directly as cells and tissues of the immune system contain melatonin receptors (Poon et al., 1994, 1993). Melatonin increases activity of T helper lymphocytes when administered to healthy participants and day length may exert changes immune processes, as well. Proinflammatory cytokines IFN-α and IFN-γ were elevated in healthy Finnish participants in the winter compared with summer (Katila et al., 1993). In people with SAD, interleukin-6 (IL-6) levels are elevated compared with healthy controls (Leu et al., 2001). Cytokines also alter plastic processes in the hippocampus (Koo and Duman, 2008; Richwine et al., 2008). Given this information, it is possible that short days induce mood changes by altering immune processes and in turn brain function. However, in individuals with SAD, light therapy failed to reverse elevated IL-6 but did alleviate symptoms, which implies that elevated IL-6 does not cause depressive-like symptoms (Bertone-Johnson, 2009). It is possible that winter depression in humans is related to other processes independent of extended melatonin secretion. In humans with SAD, reduced sun exposure during winter could lead to a vitamin D deficiency, which can manifest as depressive symptoms in vulnerable individuals (Berk et al., 2007; Stumpf and Privette, 1988). Vitamin D can be acquired through either dietary sources or exposure to UV light. Given that sun exposure is reduced in the winter at temperate latitudes, the hypothesis that vitamin D plays a role in seasonal depression is reasonable. However, the evidence associating vitamin D deficiency and seasonal depression is mixed (Bertone-Johnson, 2009). Vitamin D supplementation elevates mood in healthy individuals (Lansdowe and Provost, 1998), vitamin D deficient individuals (Shipowick et al., 2009), and individuals with SAD in the winter (Gluth et al., 1999). However, in a study with SAD patients, bright light therapy reduced symptoms, but did not alter serum vitamin D concentrations compared with controls (Partonen et al., 1996) indicating that therapeutic relief is achieved independently of vitamin D concentrations.

Another alternative possibility is that a reduction in light alters suprachiasmatic nuclei (SCN) firing to monoaminergic nuclei to induce a depressive-like phenotype. Complete absence of light damages monoamine neurons and increases depressive-like responses in male Sprague–Dawley rats (Gonzalez and Aston-Jones, 2008). Exposing animals to constant darkness is a useful model for predicting the effect of extremes in light exposure at boreal regions on human physiology and behavior. The authors propose that the lack of light alters how the SCN communicates light information to brainstem nuclei and thus alters the structure and function of adrenergic, dopaminergic, and serotonergic neurons leading to a depressive-like behavioral phenotype. It remains possible that the symptoms of SAD are induced by low levels of light altering how the SCN communicates to monoaminergic neurons. Changes in melatonin could be an epiphenomenon of reduced light in the winter and not the primary cause of SAD. One way to test this is to inhibit melatonin secretion while maintaining levels of light exposure. Melatonin is released upon adrenergic stimulation of the pineal gland, but studies using beta-blockers in individuals with SAD have yielded mixed results (Rosenthal et al., 1988; Schlager, 1994). However, it is also possible that, while inhibiting melatonin secretion, blockade of adrenergic receptors inhibits a signal transduction pathway that is important in the production of neurotrophins.
a reduction of which have been associated with depressive-like responses (Pittenger and Duman, 2008). Additionally, administering melatonin to participants with SAD simultaneously with bright light therapy does not reverse all therapeutic effects of light (Rosenthal et al., 1986). Certainly, more research is necessary to dissociate the effects of SCN innervation and melatonin on monoaminergic function and depression.

3. Conclusion

In summary, SAD is a subtype of either unipolar or bipolar depression and, although there are competing explanations regarding the development and etiology, SAD has been strongly and consistently associated with shortened day length. Model species therefore include rodents that respond to short days with increased depressive-like responses. Currently, a number of photoperiodic and nonphotoperiodic rodents respond to short days in such a manner. It remains unclear which species will serve the best model. Satisfying all validity criteria in an animal model of SAD will prove challenging. Thus, we recommend an integrative and inclusive approach to investigating affective responses to day length in rodent models. Further, given the changes in the hippocampus that are associated with major depression and animal models of major depression, researchers developing animal models of SAD should investigate morphological changes that occur as a consequence of day length. Additionally, because SAD is associated with disruptions in both spatial and working memory, both the hippocampal and prefrontal cortical may undergo fluctuations and as such, should be investigated in animal models. Both the hippocampal and prefrontal cortical perturbations are associated with disruptions in affect. Merging these two areas of research (seasonal changes in brain plasticity and day length-associated changes in affect) will be extremely important in developing an animal model of SAD. We expect that a thorough understanding of neuroendocrine, immune, and structural brain changes that occur in many species in response to reduced day lengths will reveal proximate mechanisms governing seasonal changes in affect in humans and yield new insights into the etiology and treatment of SAD.

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