The Elusive “Switch Process” in Bipolar Disorder and Photoperiodism: A Hypothesis Centering on NADPH Oxidase-Generated Reactive Oxygen Species Within the Bed Nucleus of the Stria Terminalis

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One of the most striking and least understood aspects of mood disorders involves the “switch process” which drives the dramatic state changes characteristic of bipolar disorder. In this paper we explore the bipolar switch mechanism as deeply grounded in forms of seasonal switching (for example, from summer to winter phenotypes) displayed by many mammalian species. Thus we develop a new and unifying hypothesis that involves four specific claims, all converging to demonstrate a deeper affinity between the bipolar switch process and the light-sensitive (photoperiodic) nonhuman switch sequence than has been appreciated. First, we suggest that rapid eye movement (REM) sleep in both human and nonhuman plays a key role in probing for those seasonal changes in length of day that trigger the organism’s characteristic involutional response (in certain animals, hibernation) to shorter days. Second, we claim that this general mammalian response requires the integrity of a neural circuit centering on the anterior bed nucleus of the stria terminalis. Third, we propose that a key molecular mediator of the switch process in both nonhumans and seasonal humans involves reactive oxygen species (ROS) of a particular provenance, namely those created by the enzyme NADPH oxidase (NOX). This position diverges from one currently prominent among students of bipolar disorder. In that tradition, the fact that patients afflicted with bipolar-spectrum disorders display indices of oxidative damage is marshaled to support the conclusion that ROS, escaping adventitiously from mitochondria, have a near-exclusive pathological role. Instead, we believe that ROS, originating instead in membrane-affiliated NOX enzymes upstream from mitochondria, take part in an eminently physiological signaling process at work to some degree in all mammals. Fourth and finally, we speculate that the diversion of ROS from that purposeful, genetically rooted seasonal switching task into the domain of human pathology represents a surprisingly recent phenomenon. It is one instigated mainly by anthropogenic modifications of the environment, especially “light pollution.”

Keywords: bipolar disorder, photoperiodism, seasonal affective disorder, bed nucleus of stria terminalis, NADPH oxidase, reactive oxygen species, astrocytes, dopamine A10dc neurons
INTRODUCTION

The elucidation of the mechanism subserving the remarkable phenomenon whereby patients with bipolar affective disorders (BDs) switch rapidly from one mood state to another has been identified, perhaps with forgivable hyperbole, as the “holy grail” of research in bipolar disorders (1, 2). The hypothesis presented here proposes a mechanism for the “switch process” in question. It does so by developing the physiological kinship between the pervasive pattern of seasonal modulation displayed by many species of nonhuman life and the seasonal configuration that obtains in a significant subset of patients with bipolar mood disorders (3). [Such a configuration is displayed by definition in seasonal affective disorder [SAD] (4), an entity that overlaps strongly with BD type II [BDII] (5)]. As is well known, many animal species orient themselves to the sidereal calendar by tracking the length of day or, to put it differently, the gradually changing ratio between the illuminated (photophase) vs. the dark (scotophase) portions of the day1; accordingly such a capacity is termed photoperiodic. Upon encountering a series of changing day lengths signaling the approach of the most hazardous season (generally winter), such species undertake a gradual phenotypic “switch” of their own eventuating in an involutional state contemporaneous with that season, thus maximizing their chance for survival. We will propose that these two seasonal processes, nonhuman and human, mutually enlighten each other—and indeed that their core switch mechanisms will prove to be virtually identical. Having defended that basic identity, we shall be required to explain how the pathological human condition arose out of a strongly conserved and entirely nonpathological photoperiodic ancestry.

Thus this paper has two goals. In pursuing the first, the development of the case for a generalized mammalian switch process, we assign a significant role to reactive oxygen species (ROS) of a particular provenance, namely NADPH oxidase (NOX) enzymes. Insofar as making such a claim, this position differs from one that currently enjoys favor in bipolar research: this casts ROS, viewed as stemming primarily from stressed mitochondria, as agents of damage (6–13). Without contesting the robust evidence for oxidative harm in the bipolar patient (6–13), we locate the origin of the ROS in question in a source upstream from mitochondria, i.e., the cell membrane-anchored NOX system, and in a nonpathological process involving the seasonal switch mechanism. Thus our second goal: to adjudicate between these two competing ROS-focused bipolar hypotheses.

The two ROS hypotheses need not, of course, be mutually exclusive. Indeed we arrive at a perspective which, accommodating both, allows each to hold sway at different phases of mammalian evolution. In the first and by much the longest phase, mammals exercised a “pure” photoperiodic strategy including, we believe, the ROS-based switch mechanism outlined here. It is possible that elements of this strategy carried, with modifications, into certain early hominin species (14). Yet two factors intrinsic to human evolution gradually complicated this picture. As hominins gradually migrated from the equator into temperate zones, selection pressures likely further mitigated their photoperiodic heritage so as to allow them to deal actively, not passively, with winter. Secondly, and quite recently within the Anthropocene, a different and entirely unprecedented challenge to photoperiodism has arisen: anatomically modern human beings have come to modify their own environment by generating “light pollution.” That is, through artificial light they have degraded the remarkable step-off between the lighted vs. the dark phases of the sidereal cycle upon which photoperiodism depends. This change has given admission, we shall propose, to ROS working as a damage agent rather than a player in a signal cascade.

Thus modern human beings with BDII/SAD may represent a complex amalgam featuring both constructive and destructive effects of luminance and ROS. To offer an analogy from another medical domain, the patient with congestive heart failure may exhibit symptoms through which one may detect underlying physiology: while the enlarged heart denotes a clearly pathological feature, the avid renal tubular reabsorption of sodium points to an aspect of physiology that is working only too well. Similarly, the BD patient who develops mania in autumn or spring may display delusions of grandiosity that are obviously pathological—and yet the timing of his episode will represent an atavistic remnant of his photoperiodic physiology.

Now it is mandatory to consider whether some sort of logical fallacy is involved in the application of the clinical terms mania and depression to nonhuman mammals. A possibly less contentious dimension with application both to nonhuman animals and human beings with SAD/BDII is arousal. Thus in Figure 1, a schematic diagram applying to seasonal organisms whether nonhuman or human, the baseline depicted represents the degree of arousal under non-stressed conditions; even the Syrian hamster makes seasonal excursions above and below that reference point. While the excursion into states of hypoarousal (i.e., torpor and hibernation) is well known and in fact is generally viewed as coterminous with the SD response, a preceding excursion into hyperarousal has only recently attracted attention. The Syrian hamster, for example, does not descend quietly into torpor over the months-long course of SDs. The hyperarousal phase sometimes requires artificial “editing” in the laboratory of the autumn-winter environment, i.e., a partial representation of that season including SDs but excluding a drop in temperature, for prolonged and patent expression: thus if the photoperiod is switched from LDs to SDs but temperature is kept unchanged, the hamster will enter a phase of increased aggressiveness (15–18). Clearly such organisms are hyperaroused. This behavioral phase may continue indefinitely unless decrease of ambient temperature is added to extended scotophase; only thereafter does the animal progress into torpor (19). In our view the hyperarousal phase should not be dismissed as a laboratory artifact; what is artificial is rather prolongation of this phase beyond its relatively brief naturalistic life (see below). In any event we do not lack other and more manifest examples of seasonal hyperarousal in vertebrates with some kinship to mania: these include, in larger quadrupeds, the constellation of irritability, hypersexuality, and peak reproductive potency

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1For technical terms such as photophase and scotophase, see Box 1, Glossary of Selected Terms.
Box 1 | Glossary of selected terms.

Aerobic Glycolysis (AG): a biochemical cascade that converts glucose into lactate through 10 consecutive enzymatic reactions. In the CNS AG is carried out largely by astrocytes. The qualifier aerobic means that the cascade can begin and run to completion in the presence of oxygen—something that would ordinarily cause the cell to metabolize glucose through another pathway called oxidative phosphorylation.

Crepuscule: strictly speaking, like twilight, this may refer to either dawn or dusk. In the current paper, it indicates the particular twilight time that coincides with the animal’s transition from sleep to waking. This varies as a function of the mammal’s activity pattern: for nocturnal species, it means dusk; for diurnal ones, dawn.

Crepuscule Change Detector: a homegrown term for a CNS mechanism that is tuned to distinguish day-over-day luminance changes in the pre-wake crepuscular environment, particularly in autumn as the days are getting shorter. This mechanism may involve a comparator sensitive to any difference between yesterday’s temporal activity pattern (as reflected in the comparatively inert circadian activity rhythm) vs. today’s luminance signal as sampled during the relevant crepuscular period. (The sampling process itself takes place in REM sleep.) We tentatively locate such a comparator in the DMN of the hypothalamus.

Hormesis: the concept according to which a minimal dose of an otherwise innocuous substrate or influence calls forth an answering response the beneficial effects of which clearly outweigh the potentially harmful effects of the initial or triggering dose.

Incremental Augmenter: homegrown term for a subtle CNS device that amplifies the animal’s SD response from day to day, doing so by transmitting the seasonal decision formulated within the suprapontine module to the brainstem (pons) REM sleep generator. Such a daily effect probably involves augmentation of REM density (see below).

LD or LDs: long or longer days, sometimes casually identified with those of summer. Here it has the comparative meaning longer, i.e., that portion of the calendar in which photophase is longer (and scotophase shorter) than it was on the previous day. This obtains not in astronomically defined summer but from the winter solstice to the summer solstice. NADPH Oxidase (NOX): a family of enzymes responsible for generating ROS.

In our hypothesis, one or more of these enzymes generates the ROS that mediate the switch from the first (hyperarousal) to the second (hypoarousal) phase of the mammal’s response to SDs.

Photophase: the illuminated portion of the daily cycle.

Reactive Oxygen Species (ROS): a group of highly reactive compounds deriving from oxygen. Once believed to have a largely destructive role, these have in recent years been shown to carry out physiological assignments, functioning for example within signal cascades.

REM Density: a measure of that portion of the REM sleep phase that is occupied by the characteristic rapid eye movements (REMs) after which this phase in general is named. It may be calculated directly as a percentage; an alternative, somewhat indirect, measure involves assessing the duration of individual bouts of REMs. A REM sleep phase may last 60-90 minutes in human beings; a bout of the characteristic eye movements may last from seconds to over two minutes. Greater REM density of biological significance generally means longer bouts of individual REM episodes (i.e., lasting over 2 minutes), not a greater number of short REM bouts (i.e., lasting a few seconds).

Scotophase: the dark portion of the daily cycle.

SD or SDs: short or shorter days, sometimes casually identified with those of autumn and winter. Here it has the comparative meaning shorter, i.e., that portion of the calendar in which photophase is shorter (and scotophase longer) than it was on the previous day. This is the case not in astronomically defined winter but from the winter solstice to the summer solstice.

Seasonal module: this term is utilized here to indicate a variably (loosely or tightly) linked network of subcortical nodes that, working together, mediates the seasonal animal’s response to the SDs of autumn. See Known and Likely Nodes in the Photoperiodic Network for a rough consensus concerning the neural nodes to be included within this module.

(Continued)
adjustment of arousal through both of these systems. Other nodes attested by lesioning to belong within the mammalian seasonal network include the ventromedial nucleus (VMN) of the hypothalamus (31) and the bed nucleus of the stria terminalis (BNST) (32) the anterior division of which has a major role in our hypothesis. Much evidence also implicates in seasonal function the orexinergic neuronal system located primarily in the lateral hypothalamic area (LHA) with a smaller contingent in the DMN (33–35).

Other kinds of evidence suggest that tissues within or directly adjoining the brain’s ventricular system participate in the mammalian SD response. Different members of the circumventricular organ (CVO) group along with the closely related pineal gland and choroid plexus not only secrete melatonin (the pineal gland) but also transmit the effects of leptin, a hormone with significant ties to seasonality (36), to the sympathetic arm of the ANS [the subfornical organ (SFO) (37)] and generate seasonally appropriate neurotrophic factors [the subcommissural organ (SCO) and the choroid plexus (38)]. Relevant in this connection is the discovery in 2012 by Nedergaard’s group of what they named the glymphatic system (39, 40). Before that discovery, strong seasonal variation had been documented in the brain’s transport of pertinent molecular mediators through cerebrospinal fluid (CSF) (41). Although to our knowledge investigators have not explored the seasonal ramifications of the glymphatic system, we levy that concept here to strengthen several themes which we believe relevant to photoperiodism. First, the glymphatic concept sanctions the centrality within our hypothesis of astrocytes and the gliotransmitters they produce including, as we shall see, ATP and lactate. Second, we are encouraged by the glymphatic template to blur the boundaries between the strictly circumventricular organs and other periventricular tissues that we envision as components of the photoperiodic network. These periventricular sites include not only established seasonal players such as the DMN but also other loci such as the ventrolateral periaqueductal gray (vIPAG) and the oval subnucleus of the BNST; the latter two comprise the locations respectively of the cell bodies and the main terminal field of the dopamine (DA) A10dc cell system. Thus we will not draw any strict distinction as regards seasonal function between the circumventricular organs per se and these periventricular tissues or, accordingly, between CSF and interstitial fluid (ISF). Third, the notion that glymphatic flow actively distributes astrocytic products through CSF/ISF primarily during sleep hovers in the background of our claim that the mammal carries out a crucial fluid transport component of its SD response while sleeping (though we have in mind a more differentiated portion of sleep than has obtained thus far in discussions of the glymphatic system). Figure 2 provides a simplified schematic of the photoperiodic network including the CVOs.

The Supra-2-Min Problem

The onerous nature of approximating in the laboratory the extremely slow change of naturalistic photoperiod may have led to some unfortunate shortcuts. Understandably, the classic laboratory protocol simplifies matters by comparing animals under two photoperiodic conditions, a fixed LD (e.g., 16 h of light: 8 h of dark [L: D 16: 8 where L and D refer to light and dark respectively]) vs. a fixed SD (e.g., L: D 8: 16) schedule. Such a procedure has proven useful for defining an absolute value for the minimum duration of scotophase that triggers involution, e.g., 11.5 h for the Syrian hamster. Yet no animal in the wild ever experienced two consecutive days (let alone more) of identical photoperiod. In the wild, it is the barely perceptible day-over-day extension of scotophase in late summer and autumn that must somehow be “read” by the organism and must then be integrated over a number of days. [This is compatible with the view that a series of such days, perhaps as few as 7–14, is required for the secure fixing or “memorizing” of that sensory decision (42)]. Since for temperate-zone mammals we have good warrant for the emergence in some mammals of photoperiod-driven neuroendocrine change in August (43), i.e., a month at the beginning of which scotophase is increasing by about 2 min daily, and since at such latitudes that daily extension of scotophase rarely reaches 4 min at its late-September maximum (44), we can safely assume that most effective values for day-over-day scotophase change fall on a spectrum between 2 and 4 min. For simplicity we shall refer hereafter to the effective SD signal as one with a “supra-2-min” value. This will be short for: a rate of expansion of day-over-day scotophase between an approximate minimum of 2 and an approximate maximum of 4 min.

As demonstrated by resonance or Nanda-Hamner protocols, the animal reads environmental luminance signals most efficiently when they recur with 24-h periodicity (45). This has long implied that the seasonal animal may be sensitive to such signals within a given segment of its own endogenous rhythmicity. But the definition of this segment has proven surprisingly problematic. For example, attempts were made to construe sensitivity to the slow change of photoperiod on the model of classic work establishing circadian response curves to brief pulses of light administered to animals in constant darkness and yielding immediate phase shifts. These attempts were disappointing insofar as such pulses inevitably impaired or aborted, rather than potentiating, the involutinal response (46). Evidently there is some difference between an animal’s handling of what may be termed arousing emergencies [whether involving light pulses or so-called nonphotic stimuli (47)] that immediately reset the circadian activity rhythm vs. its negotiating the slow
expansion of scotophase that takes place in SD insidiously over weeks and that is not accompanied by such resetting. Perhaps there is something amiss with the frequently unspoken assumption that the animal’s “endogenous” rhythmicity serves as a baseline upon which varying “exogenous” photoperiods impinge. What if the seasonal animal, rather than being passively subjected to the external influence of luminance change, were constantly searching for evidence of that change? And what if the search, not the mere reception of the sensory signal, transpired within a segment of its sleep cycle that was adapted for maximal sensitivity to a crepuscular grade of luminance?

In 3 papers published in 1978-1988, one group found evidence of such a possibility (48–50). The epochs of rapid eye movement (REM) sleep or, more precisely, of REMs themselves, the phasic oculomotor events after which the entirety of the sleep phase in question is named, were noted to occasion radically augmented sensitivity to a certain species of luminance-related information. Thus sectioning the extraocular muscles of rats deprived them
The photoperiodic network. The diagonal axis going from lower left to upper right features four coronal sections with the most rostral stationed at the upper right. A fifth, most caudal in the series, is placed at the lower right of the figure. Each of the five coronal sections is numbered with a red numeral (from rostral to caudal): 1 = hypothalamus at level of SCN (for abbreviations, see below); 2 = hypothalamus at level of DMN; 3 = periaqueductal gray region at level of DA A10dc neurons; 4 = pons at level of SLD; 5 = medulla at A1/C1 level. At level 3, closed green circles represent DA A10dc neurons; closed red circles, GABA neurons. At upper left, the diagram concentrates upon the aBNST but also includes, as representative of all of the circumventricular organs, the SFO. Key anatomic authorities are given in text. Terminology of BNST subnuclei generally derives from Swanson and colleagues [here, references (161, 162)]. We do not have room here or in the text for an extended discussion of the multiple cases of anatomic reciprocity joining suprapontine and pontomedullary sites. In brief, key arousal-related monoamines with cell bodies at pontomedullary levels, especially the DA neurons in the vlPAG at level 3 and the medullary NE neurons at level 5, project rostrally to suprapontine sites, especially the hypothalamic levels 1 and 2 and the aBNST. (To minimize clutter, afferents from below involving DA and NE to suprapontine regions are given for the aBNST but omitted for the hypothalamus.) Primarily at the suprapontine hypothalamic sites, the arousal-inflected monoamine systems mesh with afferents (especially those traveling in the LHRT) bearing luminance data from the retina. Neurons within the suprapontine sites then project back into the vicinity of the pontomedullary sites from which the rostrally projecting tracts originated. In brief, the reciprocating circuits of interest to us move from arousal region → luminance modulation →
of the ability to adjust their circadian activity rhythm to the light: dark cycle (49). Now the gradual "homeostatic" strengthening of REMs over the course of sleep (51–55) brings the last, longest, and most vigorous REM sleep episode—that immediately preceding the shift from sleep to waking—into temporal register with the sidereal transition between darkness and light (whether L → D for the nocturnal animal or D → L for the diurnal one). This means that the animal by means of its REMs may be probing most effectively for luminescence signals at precisely the temporal interval when luminescence is changing (see Figure 3).

Evidence developed in the interval since these rather neglected papers were published strengthens the authors’ hypothesis. Studies in cats have shown that one aspect of REMs involves the globes’ being directed downward, nasally, and not fully convergently (56); this implies irradiation [by luminescence signals detectable in sleep through closed eyelids (57, 58)] of the superior temporal retinal quadrants. These quadrants, in the Syrian hamster at any rate, harbor the very subset of intrinsically photosensitive retinal ganglion cells (ipRGCs) that projects both directly via the lateral retinohypothalamic tract (LRHT) as well as indirectly through an intermediate station in the anteroventral LHA (LHAavr) into the DMN as well as the perifornical region (PeF) of the LHA (59–63). Rapid eye movements, then, differentially irradiate segments of the retina that transmit to the hypothalamus photoperiodically salient (but not image-forming) luminescence data.

Although our purpose here is not to elaborate a full model for what may be termed the “crepuscular change detector,” i.e., that device tuned to detect the day-over-day extension of darkness into the organism’s last REM sleep episode, we note that a likely candidate for such a device may be the DMN itself, perhaps the best-attested photoperiodic node. For two data streams mandatory for such a device, one carrying luminescence data via the retinofugal LHRT (see above) vs. another carrying strictly circadian data by means of a direct projection from the SCN (64) converge here. Also consistent with a DMN location for the crepuscular change detector would be one of the earliest signs of the SD response: namely augmented sympathetic activity, including without being limited to renal sympathetic nerve activity (RSNA). Studied over many years by T. Bartness and colleagues (65–67), this increased sympathetic activity surfaces as early as day 14 of SD exposure (65). Although many supraspinal sites within the central autonomic network (68) could participate in driving such SD-related sympathetic augmentation, the DMN may have a greater claim to primacy here than another candidate, the paraventricular nucleus (PVN) of the hypothalamus (30). In summary, a relatively simple DMN-based comparator with two inputs (bearing photic and circadian data) and one output (involving modification of sympathetic activity) will serve our purposes for now.

How Would a REM-Based Luminescence Search Device Work With the Supra-2-Min Constraint?

We have yet to explain the relationship between the proposed REM search device and the supra-2-min constraint imposed by the day-over-day expansion of autumn scotophase. Whereas length of day, year over year, is an extremely reliable (i.e., nearly noise-free) sidereal quantity (69), the biological search device involving REM sleep circuitry possesses a certain degree of built-in variability, a quality which, as we shall see, permits it to undergo seasonal modification.

One important dimension along which REM sleep exhibits relevant variability involves the magnitude or saliency of REM bursts within a given REM sleep episode. This proportion is ordinarily measured in one of two ways. One may ascertain the duration of an individual REM burst; this may have values ranging between shorter (e.g., 20 s) and longer duration (e.g., 120 s) (54). Alternatively, one may measure so-called REM density, defined as that percentage of a REM sleep period occupied by REMs; the cutoff between low and high density was placed by one group at 10%; thus any value >10% would qualify as high (53). (Either definition would serve our purpose.) It may not be fortuitous that the longer-duration REM bursts satisfy the supra-2-min constraint whereas the shorter-duration ones, missing the 2-min lower limit, do not. Given that the homeostatic aspect of REM sleep causes REM density to increase over the course of a sleep episode, the last REM episode will tend to display greater REM density than those generated earlier in sleep (51–55). Yet we propose that even this last episode will fail to reach maximal REM density unless and until the pontogeniculooccipital (PGO) waves associated with REMs proper (70) summate in specified loci with luminescence data carrying a SD signature. In this case the target locus, primarily the LHA, played upon both by PGO waves (71, 72) and by the LRHT (59–63), will be excited sufficiently to trigger a neural output, here termed an incremental augmenter, that projects caudally back to the pontine REM sleep generator. We emphasize this caudally projecting element because it is critical for the
iterative development of the SD response. Only when the incremental augmenter strengthens the REM sleep generator will it produce a series of increasingly potent high-density bursts each lasting not < 2 min. That is, under naturalistically changing SD the number and length of such bursts within the 60–90 min of the final REM sleep episode will vary directly with length of scotophase.

As for the location and neurotransmitter signature of the LHA system which sends a reciprocating link back to the brainstem, one likely candidate is the LHA-based melanin concentrating hormone (MCH) system. This system is not only the recipient of the PGO waves of REM sleep (71, 72) but also disinhibits the same sleep stage by sending MCH/GABA fibers to vlPAG GABA cell bodies that in turn project to and inhibit the
The aBNST-, Astrocyte-, and NOX-based cycle: focus on the full autumnal switch. As1, As2, and As3 represent astrocytes in the aBNST; their processes envelop many of the NE varicosities which obtain in abundance here. Each astrocyte should be understood to dominate events primarily, though not (Continued)
pontine REM sleep generator (73–75). Thus the MCH/GABA projection is well placed to serve as the incremental augmenter required by photoperiodism. Of note, the interesting findings of increased REM sleep bout duration (74) and frequency (75) with optogenetic and chemogenetic stimulation respectively of MCH neurons were made in a non-photoperiodic context; our hypothesis would predict that monitoring MCH neurons in traditionally fixed LD vs SD would reveal increased MCH neuronal activity in the latter photoperiod. Better yet, such monitoring of animals under naturally changing photoperiods would discover that both MCH neuronal activity and REM density, reciprocally reinforcing each other, vary directly with scotophase duration.

For the notion of REM sleep as a probe for SDs, we have supporting evidence from research on patients with BD. Forty years ago, patients with a bipolar condition were found to display increased REM density compared to healthy controls (76); this has been repeatedly confirmed and elaborated (77, 78). To our knowledge, no particular extra-bipolar rationale for such increased REM density, which obtains in remitted as well as symptomatic individuals (77), has been proposed. The proper context, we believe, is provided by photoperiodism: the bipolar condition includes a heightened capacity for searching for, detecting, and responding to the autumnal extension of darkness. Note that although the BDII/SAD patient will be generating REM bursts at a density exceeding controls throughout the year, he or she will meet with SDs for only half of that time (and with effective SDs, i.e., those capable of instigating the SD response, for less than half of that time). Only beginning about August (see IIB) will his or her moderate-density REM episodes, meshing with a SD signature, become photoperiodically serviceable, i.e., disposed to progressive amplification of those bursts from moderate to high intensity.

By now the supra-2-min allowance has been shown to have a bifold meaning: it references both a sidereal reality, namely the decompression of scotophase in autumn, and a temporally delimited biological process, namely the daily quotient of the mammalian (not just the human) SD response. Much more needs to be done to unpack the latter and in particular to clarify how it exploits the sidereal constraint. To make progress on this front, we need to understand the seasonal contribution of the astrocyte.

**THE SUPRA-2-MIN PROBLEM REVISITED:**

**DOES AEROBIC GLYCOLYSIS OFFER A SOLUTION?**

**A Seasonal Role for AG**

Let us pursue the notion that the seasonal animal can sense some relevant aspect of photoperiodic change within a single SD sidereal cycle. We now submit that the supra-2-min allowance gives us a clue to the nature of the molecular mediators put into play in this interval. Recall that those mediators have two tasks: they must both register the relevant change within one sidereal cycle; over a succession of cycles, they must also amplify and fix that change.

A still not fully understood aspect of photoperiodism, the seasonal animal’s metabolic modification in autumn, may offer a relevant constellation of molecular mediators. In autumn many mammals including human beings develop noteworthy alterations in glucose metabolism, often involving a mild increase in serum glucose and multiple changes suggestive of more profoundly altered central glucose metabolism. Interestingly, a small cluster of cells in the amBNST now appears to play a major role in generating a spike in glucose (79). Autumnal modifications in glucose metabolism cut across differences in photoperiodic species between those active nocturnally vs. diurnally, between obligate vs. facultative hibernators, and between nonhuman species vs. humans (80). One previously proposed reason for such autumnal metabolic change, that animals must maximize carcass fat to provide fuel for overwintering, works well for the Syrian hamster, a species that gains body mass in SD, but poorly for the Siberian hamster, one that loses body mass in SD (81). We have recently advanced an alternative suggestion, namely that the glucose requisitioned in autumn is shunted within specified seasonal CNS loci into the so-called aerobic glycolysis (AG) pathway so as to yield a number of end-products including but not limited to lactate and ATP (80). Intriguingly, the glycolytic pathway, much more active in astrocytes than in neurons (82), generally runs to completion within some 2–4 min (83, 84). Since glycolytic products including lactate and ATP can feed back powerfully within the glial syncytium to potentiate an initially weak signal (see below), AG may comprise the iterative generator of substances that not only label SDs as such but also gradually amplify the originally marginal SD signal.
Aerobic Glycolysis as an Interval Timer
We are proposing that the relationship between the time taken for AG to run to completion inside astrocytes and the temporal extension, from 1 day to the next, of autumn scotophase is not fortuitous. In other words, successful completion of AG serves in the initial phases of the autumnal response as a surrogate for the supra-2-min sidereal SD signal. Thus AG in itself may be said to comprise a mechanism long intuited as necessary for seasonal physiology but rarely given a concrete housing either molecular or anatomic: an interval timer (85). Yet the timer as elaborated within our hypothesis differs in a crucial respect from the classic one: students of seasonality generally ascribe to the interval timer construct the capacity to distinguish an absolute duration of time, e.g., that which in the Syrian hamster labels a melatonin pulse as exceeding 11.5h and thus as competent to trigger the SD response. Our interval timer, on the other hand, is a comparative one, measuring the difference between yesterday’s duration of scotophase and today’s and, when that difference regularity exceeds 2 min, inviting the organism to roll out or continue its SD involutorial process. Thus it is not only AG as such that allows us to highlight the role of astrocytes in photoperiodism: it is also the relatively slow temporal scale, measured in minutes, on which astrocytes carry out certain functions vs. the millisecond scale preferred by neurons (83, 84) that renders the former cell type a central actor in seasonality. Before turning to the role(s) of AG in the seasonal network downstream from its interval timer function, we need to understand the molecular factors that contribute to the successful accomplishment of this cascade.

To drive glucose through the AG pathway, the astrocyte requires sequential or near-simultaneous stimulation of two different second-messenger pathways, one involving calcium signaling and the other cyclic AMP (cAMP). This has recently been demonstrated clearly for NE through α1 receptors it activates a calcium signal that sets AG in motion; through β2 receptors it activates CAMP which serves to prolong and maintain AG (86). Dopamine is capable of the same complex yoking of calcium and cAMP signal cascades, stimulating the former in part through nonreceptor-based means (see below) and the latter primarily through the D1 receptor. The “synarchic” linkage of calcium and CAMP cascades, one that also figures in a number of nonphotoperiodic contexts, e.g., insulin granule exocytosis (87), will prove useful when we explore the anatomy of the seasonal response. Now both NE and DA are generously represented within the circuitry outlined above—especially within the aBNST node which likely harbors the greatest density of NE fibers within the mammalian brain (88). Yet while NE and DA are, we believe, the primary photoperiod-dependent activators of AG in the aBNST, they are not the only ones. This complex region serves as a convergence point for a number of peptides with the capacity for “synarchic” coordination of calcium and CAMP cascades. Of these, we mention only VIP which besides possessing that dual capacity (89, 90) projects to the aBNST from several loci (91–93) including the vPAG. There, it colocalizes with a subset of DA A10dc neurons adjoining the cerebral aqueduct (94) and, significantly, aids in organizing REM sleep (95). To simplify matters, we largely ignore these peptidergic supporting actors, focusing instead on the aBNST-resident monoamines. We now turn to the aBNST itself, a region that, we believe, plays a central role in sculpting the mammal’s response to autumnal SD including its capacity for bivalently modulating arousal.

THE ANTERIOR BED NUCLEUS OF THE STRIA TERMINALIS (ABNST) AS A SUBSTRATE FOR GLYCOLYSIS-DRIVEN SEASONAL STATE CHANGES
Arousal-Related Switches Implicating the BNST
In recent years the aBNST has received escalating attention as a substrate for mood disorders (96). Further, it has decisively been implicated in at least two different forms of nonseasonal phenotypic switching, each involving the dimension of arousal. First, it is now well established as a locus for a species of neurobehavioral switching that appears an almost inevitable component of drug abuse. The strong DA A10dc projection into the anterolateral BNST [aBNST], especially the oval subnucleus (97, 98), clearly participates in drug-induced hyperarousal (99) many symptoms of which have obvious similarities to manic euphoria (see below). Yet induction of hyperarousal by drugs such as cocaine is regularly succeeded by a negatively valenced state of withdrawal, frequently amounting to frank depression (100, 101). While the circuitry underlying the negatively valenced state remains less clear than that subserving the hyperarousal phase, a leading candidate is the medulla-based NE system that ramifies densely within the anteromedial BNST (amBNST) (102, 103). (For both NE and DA projections to the am- and aBNST respectively, see Figure 2) Similarly, the same NE→ amBNST circuitry provides a key component of the involutorial syndrome that follows classically upon infection (“sickness behavior”) (104). Each of the amBNST-affiliated hyperarousal phenotypes is strongly reminiscent of the involutorial phase of the SD response. (The classic hypersomnia of the typical SAD patient in winter is also a feature of “sickness behavior.”) We thus have preliminary warrant to align DA- and NE-driven aBNST events with the hyper- and hypoarousal phases respectively of the SD response. Since the autumnal organism begins with hyperarousal as a preamble to involution (see Introduction and Figure 1) and since DA is frequently identified as a sponsor of arousal, we begin with DA and the aBNST.

Hyperarousal First: The Work of DA in the aBNST
Dopamine has long held pride of place as a molecular correlate of the manic phase of bipolar disorder (105). Pressured speech, hyperkinetic motor behavior, insomnia, euphoria, elevated libido and propensity for reckless behavior, all classic signs of the manic episode, have collectively been referred to increased activity of midbrain DA systems, generally (for motor function) those based in the substantia nigra and (for non-motor aspects) the A10 neurons housed largely in the ventral tegmental area (VTA) (105). Less clear has been the contribution of individual DA A10 subsets. One candidate worthy of consideration is the DA
A10dc cell group, that which projects lavishly into the aBNST and especially into its oval subnucleus (97, 98). As noted above, dopaminergic activity within the oval subnucleus correlates closely with the hyperarousal driven by cocaine and related street drugs (99). And the A10dc neurons support the long-sought dopaminergic contribution to the daily waking phase (106). Particularly relevant to the autumnal hyperarousal both of classic photoperiodic animals and of the human being with SAD is the proximity of A10dc neurons to the cerebral aqueduct (94, 97, 98). For this location renders them susceptible to modulation by CSF-borne melatonin which stimulates CAMP but only when its pulse is prolonged by SD (107). Furthermore, DA A10dc cells insofar as overlapping with the dorsal raphe nucleus may in some species comprise a target of a direct retino-raphe projection (108, 109) or a more recently defined indirect retino-vPAG visual circuit (110). Perhaps most relevant to our model is the promise of the A10dc→ aBNST system as an incremental amplifier of arousal.

Dopaminergic fibers in the aBNST (97, 98) and elsewhere in the brain display a predominantly nonjunctional form of release, i.e., their release sites tend not be in apposition to postsynaptic receptors (111, 112). Once liberated from A10dc varicosities, DA promotes calcium shifts in astrocytes through both receptor- and non-receptor-based means, driving the latter through a step involving ROS created through autooxidation of DA itself (113, 114). The resulting calcium signals can directly trigger AG and, subsequently, extracellular release of gliotransmitters including lactate, ATP, and glutamate (115). In the nucleus accumbens, closely connected to the BNST (116), ATP release, augmented by hyperglycemia and insulin, subsequently liberates additional DA by acting through a P2Y receptor on DA terminals (117), illustrating positive feedback at the signal cascade level (DA→ ATP→ DA). Dopamine also impinges directly on BNSTov neurons bearing D1 receptors; these include corticotropin-releasing hormone (CRH)/GABA neurons which augment arousal (98). Furthermore, its likely modulation by both lumiance and melatonin (see above) combined with its projection upon the LHA (106) renders the DA A10dc neuronal group an attractive candidate for the lumiance-inflected vector that summates in autumn inside the LHA with the REM sleep-inflected vector, thus activating the LHA “incremental augmenter” (see How Would A REM-Based Luminance Search Device Work With the Supra-2-Min Constraint?). Thus both directly and through the intermediary of astrocytes, DA release within the aBNST and other seasonal nodes could account for slowly growing organismal arousal through the entire pre-switch phase.

Another pro-arousal mechanism possibly allied to DA may involve the daily glucocorticoid (GC) pulse profile. Recall that sympathetic hyperactivity involving increased RSNA activity surfaces by 14 days of SD exposure and continues throughout autumn and winter (see The Supra-2-Min Problem). A cognate species of sympathetic activity, one mediated by the thoracic splanchnic nerve, impinges on adrenal and more specifically HPA activity (see Figure 3). This likely accounts for the phase-advanced and/or augmented GC pulse frequently displayed in autumn by photoperiodic animals (118–122) as well as by the bipolar patient (see below). Interestingly, healthy adult humans display a strikingly phase-advanced salivary cortisol profile, although no alteration in amplitude, in winter vs. summer (123). In augmentation both of HPA activity and of autonomic (sympathetic) drive, the aBNST clearly plays a part although linkages between these two arousal-related effects and precise subnuclear contributions remain elusive (124–126). Without developing the case at length, we propose that ultimate responsibility for augmented SD sympathetic activity, whether that of interest to the Bartness group (see IIB) or that which phase-advances the GC pulse, rests with the DA A10dc projection into such established central autonomic nodes as the LHA and the aBNST.

As for bipolar patients, studies of their seasonal GC profiles have at times failed to distinguish early SD (i.e., autumnal) from late SD (i.e., winter) events. For example, one frequently cited paper on GC pulse dynamics in seasonally depressed SAD patients found a radically blunted GC curve (127); given that all serum samples were drawn no earlier than November, this testifies clearly to the later (i.e., winter), not to the earlier (i.e., autumnal), development. We suspect that the earlier, peri-equeinoxial, situation involving the hypomanic SAD patient would resemble the previously noted GC profile in mania at large, i.e., elevated and/or phase-advanced (128, 129). Of special note is the significantly augmented GC pulse in patients with “dysphoric” mania (130, 131), an endophenotype for which the early SD aggressiveness of smaller photoperiodic mammals (see Introduction) may serve as a model. In any event the seasonally modified GC pulse bears crucially in two ways on DA dynamics as we approach the switch itself.

First, the degree of phase-advance of the GC pulse in the SD organism, whether classically photoperiodic or bipolar, is on the order of 30–60 min (118–122, 128, 129). Such a phase-advance causes the GC acrophase to migrate across the border separating waking from sleep. Thus instead of falling some 15–20 min into the waking phase, the pulse acrophase in SD is brought squarely into the center of the concluding epoch of sleep—i.e., the last, longest, and most vigorous REM sleep episode (see Figure 3). Of note, GCs are potent magnifiers of astrocytic calcium waves (132). This attraction of the GC pulse acrophase into late sleep, which we see as a key precursor to the switch process, amplifies calcium wave activity already instigated in aBNST astrocytes by DA. At least at first, such signaling would promote yet further release of DA.

The second effect of the modified GC pulse in SDs with implications for DA release stems rather from its augmented amplitude than from its phase-advance. As Gasser and Lowry have shown in detail, GCs powerfully inhibit the organic cation transporter (OCT), a high-capacity, low-affinity transporter mediating uptake of DA as well as serotonin (5HT), NE, and histamine (133). Interestingly, the distribution of the OCT3 overlaps significantly with the seasonal network, with strong

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2We cannot discuss within the confines of this paper an apparent conflation here of REM sleep arousal with waking-phase arousal. Doing so would involve adumbrating the increasingly well-documented stimulatory effect of midbrain DA neurons upon REM sleep. Dopamine, we believe, sequentially or simultaneously activates both forms of arousal.
representation in the DMN, the PeF, and the CVOs (134, 135). Such inhibition of the major high-capacity transporter of DA by GCs means that DA concentration (as well as that of other relevant monoamines) will remain significantly augmented within seasonally relevant nodes roughly during the acrophase of the GC pulse, i.e., during the last and longest REM sleep episode. Analogously, mice with reduced activity or knockout of the low-capacity, high-affinity DA transporter (DAT) display hypersensitivity to change of photoperiod, thus furnishing one of a small number of persuasive animal models for bipolar disorder (105, 136–138). One could pursue this promising and relevant model by developing a prototype that integrates both transporter species, the DAT and the OCT3.

Glucocorticoids, then, previously incriminated in the switch process (139), may be said to shift the nature of subcortical processing in SD both by augmenting astrocytic calcium signaling and by elevating monoamine levels3 within the glial syncytium. Although by promoting DA release this shift may initially support the hyperarousal phenotype [a well-known effect of exogenous GCs (140)], it may also serve as forerunner to the involutional state.

Into and Through the Switch, a New Actor: The NOX Enzyme Family

We have already mentioned, as preliminary warrant for considering a link between seasonal involution and the NE-aferented amBNST, two other involutional phenomena connected with the amBNST, namely the quasi-depressive phase which succeeds drug-induced arousal and the “sickness behavior” precipitated by infection (see The Supra-2-Minute Problem). Our task here is to explore the possibility of a BNST-based mechanism by means of which the seasonal form of involution comes about. In perhaps simplistic terms, how does the action of DA in the aBNST get communicated to that of NE in the amBNST? And how does its behavioral polarity get reversed in the process?

It is at this point that NOX enzymes and their ROS product come into view. That ROS have a role in seasonal switching is hardly novel. Indeed NOX enzymes, which have a long evolutionary history (141), participate in seasonal modulation of life forms including many plants (142) and invertebrates (143) that evolved well before mammals. And in amphibians NOX-derived ROS contribute to different kinds of phenotypic switching at large (i.e., not specific to photoperiod) such as that involving Xenopus tadpole tail regeneration (144) and amphibian metamorphosis (145). Until recently, their position in mammalian photoperiodism has been less clear. However a physiological role of NOX-derived ROS has emerged over the past decade with regard to mammalian neurogenesis—and here we approach links to seasonality proper.

The phenomenon of neurogenesis—the differentiation of a stem cell into a neuron—may represent the most radical form of CNS plasticity. Research on DA neurogenesis suggests that the key DA progenitor/stem cells tend to arise in the dorsocaudal midbrain, i.e., roughly the region that eventually will house the DA A10dc cells. They then migrate from that location to populate the sectors that with maturation of these progenitors will become the substantia nigra pars compacta and the VTA (146–149). Significantly, one powerful influence upon neurogenesis involves photoperiod (150). Now DA neurogenesis appears to have a tropism for SD that cuts across distinctions based on breeding season (151). Why should neurogenesis be conjoined temporally with the involutional phase? At least a proximal answer may involve the roles which amBNST NE plays in both of those processes.

As recently emphasized (152), the noradrenergic β2 adrenoreceptor (β2AR) affords a functional link between NE and NOX activity. While clinical applications have heretofore been limited, such a link sets the stage for understanding how NE may contribute to the prosurvival phase of the SD response. Working through ROS, NE is well poised to drive activation of one of the major neurotrophic substances, brain-derived neurotrophic factor (BDNF), which in turn safeguards the viability of DA neurons (in this case, through winter) (153). Now although NE itself can directly activate transcription of BDNF (154), its role in the seasonal narrative would be more subtle: it would begin by transactivating, through ROS, the TrkB receptor, one of the two main receptors for BDNF. Such transactivation — the activation of a receptor tyrosine kinase independently of the presence of its traditional ligand (155)—is well suited to the incremental nature of the SD response. For transactivation of a RTK yields a more modest response than ligation by the traditional agent (in this case, BDNF) (155); this accords with the initially imperceptible beginning of the SD response. Direct signaling by BDNF protein, known to be transported in anterograde fashion from the lateral parabrachial nucleus (LPBN) to the aBNST (156), would follow at a later stage. And if in early life the BDNF carried by NE fibers to the ventral midbrain DA progenitor cells promotes DA neurogenesis (157), in maturity the same ligand could account for the neuroplastic (if not frankly neurogenic) effects, i.e., those involving a neurotransmitter switch, now well documented in photoperiodism (158–160). Through its potent bidirectional connections with both hypothalamic (161) and brainstem (162) arousal sites, the aBNST thus offers possibilities not only for rapid-response modulation of arousal but also for participating in slow transport of neurotrophic ligands such as BDNF4.

The neuroplastic/neurogenetic potential of the aBNST is not likely to be limited to that driven by NE. We can only glance at one of several other promising conduits for neurogenesis in the BNST and connecting regions, namely that involving the fibroblast growth factor (FGF) family of neurotrophins. Reactive oxygen species themselves are capable in the retina

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3The role of the monoamine serotonin in seasonality, a topic which has received much attention, cannot be addressed here.

4Note that the role posited here for BDNF within the involutional phase appears to contradict that which this neurotrophic factor frequently has in mediating antidepressant treatments (not limited to medication). The contradiction disappears once we take into consideration the circuitry involved. Nearly all the studies of the antidepressant role of BDNF involve the hippocampus; conversely, the involutional (simplistically, pro-depressant) activity in our model involves the BNST portion of the central extended amygdala. These two circuitries have different and sometimes opposed responsibilities. This stems in part from their radically differing NE innervation: the LC provides the entirety of the hippocampal NE; the medullary NE system supplies nearly all of this monoamine to the BNST.
and elsewhere of directly transactivating the FGF receptor and thus underwriting a prosurvival program (163). Indeed FGF neurotrophins serve as regulators of stem cell pluripotency (164) and have a growing role in seasonality given that FGF21 in particular figures in SD responses including torpor (165) and hibernation (166). The number of possible activators of NOX enzymes and of downstream permutations renders it hazardous to arrive at a possible sequential order for events pertaining to NOX-derived ROS generation and succeeding signaling events over the many weeks of the mammalian SD response. Nevertheless in Figure 4 we venture to propose such a temporal order with focus on NE, GCs, and angiotensin II (AII) as activators of aBNST NOX and of the seasonal switch. Here we depict ROS as products of astrocyte-based NOX enzymes; once created, these ROS may then be active both intracellularly and, after transport through aquaporin channels into ISF (167), extracellularly as well.

REM Sleep-Related Acetylcholine as One Guardrail Delimiting Seasonal Events in the BNST

As we have suggested at intervals, the generation of ROS within an animal brings with it significant risks; while carrying out their physiological assignment, they may cross over into pathological territory. The seasonal animal has two ways of addressing this risk. It can (a) generate a robust antioxidant response or (b) actively limit the production of ROS. Postponing the topic of (a) for now, we address (b) here—the confining of ROS generation to as modest a spatial and temporal footprint as possible. This implies fencing seasonal ROS production spatially within the defined photoperiodic module and temporally within one particular tranche of circadian activity, namely REM sleep. We now tie up a loose end by proposing that the acetylcholine associated with REM sleep has an important “guardrail”...
assignment concerning this spatiotemporal strategy. In doing so we connect with an older theory concerning bipolar biology.

Cholinergic fibers originating largely within two brainstem cell groups, the pedunculopontine tegmental nucleus (PPN) and the laterodorsal tegmental nucleus (LDT) (168) ramify densely through the amBNST but fail to enter the oval subnucleus of the aBNST (169). Although no longer considered an exclusive driver of REM sleep, cholinergic activity associated with these 2 pontine nuclei remains an important actor within that sleep phase. Increased cholinergic activity in REM sleep, often greater than in waking (170), is well placed to facilitate NE release within this division of the aBNST through a nicotinic presynaptic action on the abundant NE varicosities here. If one grants the assumption that such presynaptic stimulation of NE generally requires cholinergic levels consistent with REM sleep, then we may conclude that the NE ultimately responsible for generating neurotrophic factors such as BDNF in the amBNST is released within but not outside of REM sleep. Note that such spatiotemporally restricted release of NE within the amBNST, no doubt the result of vigorous calcium signaling here, may transpire independently of action potentials triggered within the noradrenergic neurons projecting to the amBNST. Such “chemical” stimulation of NE release independently of action potentials has been documented in the aBNST (171). Our model thus respects the finding that the ventral medullary NE neurons are as electrically silent in REM sleep as those in the LC (172). Further, the PPN/LDT → amBNST cholinergic projection (omitted from Figure 2) likely takes part in a recursive anatomy including an incremental augmenter running parallel to the one proposed earlier (see IIC). For neurons in both the al- and the amBNST return a projection directly to the PPN (173) and LDT (174). This pathway offers the seasonal module another means of iteratively amplifying some component of REM sleep such as REM density6.

Such a function for ACh in tightening the intimate relationship between the SD photoperiodic response and REM sleep (which obtains according to our model in seasonal mammals at large) bears a qualified resemblance to that which it has in the bipolar model proposed some years ago by D. Janowsky (175). [The latter model applies only to human beings with BD although a similar conception finds support in recent work pertaining to seasonal animals (176)]. According to the Janowsky model, cholinergic activity comprises a prime mover of the depressive phase of BD. At first glance at least, our model does something similar in that cholinergic activity provides a proximate cause of the NE release that in turn drives neurotrophic factors affiliated with depression. Yet in our model Ach ultimately does something more ambitious. For insofar as clearly upstream from the NE/NOX/neurotrophic axis, ACh in effect functions as an integral part of the switch mechanism. That is, it contributes to a process of slow maturation involving NE release which chronologically precedes and partly causes

5Since the GC pulse contributes materially to calcium signaling, its proposed relocation under SD into REM sleep (see IVB) suggests that it takes part along with other actors in restricting vigorous NE release to this sleep phase.

6For convenience, we overlook certain complexities in the manner in which REM sleep-affiliated Ach stimulates NE release. This likely involves an astrocytic intermediary and subsequent discharge of glutamate onto NMDA receptors which are plentiful on NE terminals in the amBNST. These complexities in no way hinder the proposed linkage of NE discharge into the amBNST with REM sleep. Finally, the rather striking step-off in Ach fiber density going from the am- to the aBNST (i.e., from generous to nearly absent) is consistent with the animal’s maintaining a measure of independence between two different vectors, one associated with REM sleep and the other with a luminance signal, segregating with the aBNST and amBNST respectively (for these vectors, see IVB). True, these signal trajectories were represented as summing under specified conditions within the LHA in order to inaugurate the SD response. But that is a contingent matter, emerging only when a SD luminance signal coalesces with a REM sleep signal. It would be counterproductive to link the REM sleep vector constitutively to the luminance vector. And so cholinergic fibers avoid the oval subnucleus, closely connected, in ways noted above, with processing of luminance signals.

**Box 3 | Main Features of the current photoperiodic hypothesis.**

1. In photoperiodic mammals, one function of REM sleep involves active search, within the last and longest REM sleep episode, for evidence of changing luminance signals, i.e., an incursion into that episode of a scotophasic longer than that which obtained on the previous day. (See “Crepuscule Change Detector” in Box 1.) The animal’s encountering such evidence when of sufficient magnitude activates a gradual process of involution that will take weeks to mature.

2. As one consequence of the animal’s SD response, DA neurons in the A10dc subset release DA into the neuropil of the alBNST, their primary target. This leads early on to functional recruitment of the aBNST into the seasonal network. At the same time these DA neurons increase calcium signaling in the aBNST and thereby activate AG in astrocytes.

3. Subserved primarily by the dopaminergic projection into the aBNST, the hyperarousal phase of the SD response (analogous to the mania or hypomania of bipolar patients) ensues. This involves daily augmentation of the amount of DA liberated within the aBNST. During this time spatiotemporal boundaries to the activational process are defended insofar as AG is activated and its products distributed only in REM sleep and only in the seasonal module.

4. At some point, certain subtle changes begin to prepare a phase reversal in the behavioral polarity of the seasonal animal. Schematically, this may involve a shift in the prime staging area of the SD response from the al- to the amBNST and from DA to NE as a presaging monomaniac. On the neuroendocrine front, phase-advance of the GC pulse leads to its full attraction into REM sleep and thus to maximal signaling of GC-sensitive elements, particularly astrocytes, within the amBNST. Maximal presynaptic release of NE here through “chemical” depolarization liberates NE, working through the β2 adrenergic receptor, which in turn drives NOX enzyme assembly and generation of ROS. Working as part of a well-defined signal cascade, these ROS begin to transcribe a prosurvival genome set including neurotrophic factors such as BDNF and FGF. The ensuing genomic shift may be described as one from a proliferative to a neuroplastic/neurogenic gene program. Dissemination of neurotrophic factors through the glial synecum and through anterograde neuronal transport conduces both to the survival of DA neurons and to their reversible functional decline consistent with the involutional phase of the SD response.

5. Hominid species gradually had to curtail full adoption of the seasonal program. Nevertheless a modified photoperiodism may have obtained among the aBNST and amBNST respectively (for these vectors, see IVB). True, these signal trajectories were represented as summing under specified conditions within the LHA in order to inaugurate the SD response. But that is a contingent matter, emerging only when a SD luminance signal coalesces with a REM sleep signal. It would be counterproductive to link the REM sleep vector constitutively to the luminance vector. And so cholinergic fibers avoid the oval subnucleus, closely connected, in ways noted above, with processing of luminance signals.
the involutional phase—originating, in ways that remain to be fully determined, within the hyperarousal stage that serves as preamble to involution (Recall that NE has a hand in the AG which figures in both phases). Our model thus addresses a weakness in the Janowsky model highlighted in a recent review, namely that it does not in and of itself account for the switch process (175). Far from claiming too much for cholinergic activity, the Janowsky model did not claim quite enough.

To summarize the argument of Section The Anterior Bed Nucleus of the Stria Terminalis (aBNST) as A Substrate for Glycolysis-Driven Seasonal State Changes to this point, the general seasonal mammalian switch centers on a BNST-grounded, NOX-assisted, and REM sleep-delimited mechanism. This mechanism closely resembles or may be identical with that which governs the switch, as described by students of neurogenesis, from a proliferative to a neuroplastic/neurogenic program (146–149). Although human beings with BDII/SAD hardly inherited the entire photoperiodic constellation, they did retain, we have argued, the core seasonal switch process. Thus through their complex symptomatology we may discern a significant remnant of the bifold modification of arousal evident in nonhuman seasonal mammals. It may be proposed that the human aBNST, like that in nonhuman organisms, stages the turn from manic hyperarousal to depressive—and prosurvival—involvement.

Revisiting Once More—and Transcending—the Supra-2-Min Condition

By invoking a robust transcriptional component, especially in regard to the generation of neurotrophins BDNF and FGF, as contributing to the seasonal switch from hyperarousal to involution, we may seem to have violated our own earlier stipulation involving a supra-2-min constraint on biochemical cascades pertinent to SD. For transcriptional events, of course, must be measured in hours and not minutes. Yet the contradiction is superficial. Photoperiodism operates simultaneously within two different time frames, the first involving rapid and nongenomic events and the second transcriptional events. We have abundant evidence that a rapid and nongenomic response can not only coexist but indeed mesh seamlessly with a later genomic one. Of note, some of the most striking marriages between nongenomic and transcriptional responses involve GCs (177). Indeed a full third of cases of GC-driven transcription pass through a rapid nongenomic stage (178). And DA signaling through D1-D2 heteromers leads to a dramatic cytosolic calcium signal followed within hours by transcription of the BDNF gene (179). Further, it should not be surprising that the late SD phenotype differs strikingly from the earlier one.

For the seasonal organism, as we have emphasized, must limit some of the dangers intrinsic to the early phases of the SD response. We have previously reviewed several ways by means of which the photoperiodic animal minimizes the production footprint of ROS. Here we discuss its investment in a complementary strategy, namely the development of a robust antioxidant response. Not so paradoxically, many of the agents and processes mentioned in conjunction with the current ROS hypothesis may themselves function as antioxidants. This includes NE itself (180) and CRH (181). Above all perhaps, a family of antioxidant responses building on several sequential transcriptional steps must eventually come into play. The Nrf2 transcription factor, itself activated by BDNF, proves crucial in developing such responses (182). We cannot discuss here how events downstream from Nrf2 include not only the development of an antioxidant system narrowly defined but also promotion of behavioral involution. Such a powerful system evolved not to extinguish ROS but rather to increase their specificity as neurotrophic signaling agents while at the same time guarding vigilantly against off-target effects. The notion of an oxidative trigger as a means of stimulating a complex response (including but not limited to an antioxidant program) is consistent with the general concept of hormesis. According to this concept, a relatively low and transient dose of an otherwise noxious substance calls forth a response the beneficial effects of which outweigh the risks associated with the initial trigger (183, 184). Yet whether such a beneficial arrangement would survive nontrivial modification of the luminance environment in which it evolved is another question.

Adjudicating Two Views on ROS and Related Inflammatory Mediators in Bipolar Disorder

Certain off-target effects of ROS signaling may have surged into prominence surprisingly recently. Mammalian photoperiodism was likely well advanced by some 50 million years ago amongst the small species proliferating in the Cenozoic era (185). Given the non-negligible remnant of seasonal modulation in modern man, it is conceivable that a somewhat more extensive version of photoperiodism obtained in an earlier hominid species. Indeed a plausible case has been made that Neanderthals exercised a general photoperiodic capacity (14). Yet even if that preliminary brief should prove true, this only postpones the question why part of the seasonal machinery was diverted into pathology. Conceivably the very sensitivity to luminance signals which grounds traditional photoperiodism would serve as an invitation to pathology were such signals delivered excessively or on an aberrant schedule. Particularly worrisome would be a luminance pattern that degrades the profound point of rarity between light and darkness that obtained until well into the Anthropocene. Indeed we have evidence that contamination of deep scotophase by man-made light can prove neurotoxic (186–188). With anthropogenic “light pollution,” then, ROS of the destructive kind may have entered into competition with the physiological species.

This brings us to the relationship between the hypothesis presented here and a lively current topic, namely that of “neuroprogression” in BD. As applied to BD, neuroprogression means the cumulative damage, over multiple episodes, wrought within the bipolar brain by inflammatory processes including oxidative ones. As such, this topic recapitulates and focuses the theme of ROS as damage agent, integrating this with material on related mediators of chronic inflammation. As noted at the outset, there is no reason to doubt the robustness of the evidence for damage to the brain of the patient with BD—especially the
one who has experienced multiple episodes. Yet it seems to
us that students of bipolar neuroprogression generally fail to
consider the possibility that the inflammatory cascade driving
the destruction of brain tissue represents an adulterated form
of a normative—in our view, a seasonal—survival strategy.
If, however threatened presently, that strategy has held sway
for 99+% of the time that mammals have existed on earth, it
becomes imperative to understand the nature of the connectivity
between the original pro-survival template and its apparently
recent divergence into pathology. We can begin by noting
that certain factors apart from ROS are common to both of
these developments.

One of these involves insulin resistance. Recent exciting work
suggests that insulin resistance is at the core of the insidious
decline comprising bipolar neuroprogression (189, 190). Yet
insulin resistance also figures in the SD response. In developing
our hypothesis, we have mentioned only some facets of the
role of insulin and related agents. Highlighted, for example,
was the hyperglycemia of the autumnal mammal, something
that cuts across many different variants of photoperiodism (see
A Seasonal Role for AG). Left unmentioned was a role for
concurrent insulin elevation, attested in ground squirrels by a
4-fold increase in September-October (i.e., in prehibernation)
(191). This has been viewed as linked with peripheral insulin
resistance and facilitation of prehibernation weight gain (192).
Thus mammalian hibernation has been put forward as a
reversible model for the insulin resistance of type 2 diabetes
(192, 193). While almost surely comprising a common part of
the SD response, prehibernation weight gain does not apply
to all seasonal mammals (see A Seasonal Role for AG); thus
we suspect another role, applicable to mammals in general, for
autumnal insulin spiking. One such role, central rather than
peripheral and more directly opposite to our model, would
involve a concerted action, along with insulin growth factor–
1 (IGF-1), upon glucose uptake by astrocytes (194, 195). With
entry into the brain and indeed astrocytes, we gain admission to
a feature that distinguishes constructive from pathological ROS,
glucose, insulin, and insulin resistance—the possibility of cycling.
For cycling on a seasonal plane is precisely the solution that
photoperiodic mammals began to exploit in the late Mesozoic so
as to keep inflammation to an absolute hormetic minimum—so
as not to enter upon the slippery pathway to cumulative damage.

In summary, our theory makes three predictions regarding
the nature of the relationship between seasonal vs. pathological
insulin resistance (and related inflammatory mediators including
ROS). First, it suggests that a point of rarity, evolutionary and
otherwise, may be discerned between these two processes.
Despite significant overlap at the molecular level, an overlap
that permits us to understand how and why the two are
connected at all, significant damage obtains regularly in the older
bipolar patient but rarely in the seasonal nonhuman mammal.
Second, no differentially acting factor explaining the difference
between these two outcomes need be invoked other than that
involving two variants of lumiance signaling—scrupulously
photoperiodic vs. degraded or corrupted 3 . Third, the seasonal
form of insulin resistance sorts with the cyclical generation
of ROS by NOX enzymes whereas the pathological version
sorts with ROS release in adventitious and “noisy” fashion
from damaged mitochondria. In Box 2 we propose several
experimental approaches whereby these predictions may be
tested.

CONCLUSION
How Does the Current
Photoperiodic/Bipolar Switch Hypothesis
Differ From Previous Ones?
Our approach to the problem of the photoperiodic/bipolar switch
process separates from previous ones in three ways. First, it
establishes a more detailed fabric of continuity between the
classic photoperiodic animal and the seasonal bipolar patient
than has obtained thus far. The common denominator linking
these two mammals resides less in the particular features
of the organism at a given season (hypersomnia can only
metaphorically be termed pathology) than in the hinges or
transition points separating the seasons from each other. Thus
the articulation between autumn and winter involves roughly
the same switch-related signal cascades in the Syrian hamster
and the human being with BDII/SAD. Highlighting the role within
these cascades of NOX-derived ROS marks a divergence from
the current emphasis in BD research upon ROS as agents of
pathology. As noted above, the two aspects of ROS may well
coexist in the modern patient: the first or constructive aspect,
dominant throughout mammalian evolution until the very latest
phase of the Anthropocene, may by means of its exquisite
sensitivity to ROS have prepared for the advent of the deleterious
kind. It will take work to disentangle, within that patient, the
relative contributions of the two.

Second, we have proposed partly novel conceptualizations of
the roles both of REM sleep and of astrocytes in mammalian
photoperiodism at large. Rather than responding passively to
siderial change, the mammal in our formulation searches actively
and continuously for evidence of such change during the
crepuscular interval which necessarily coincides with its last and
longest REM sleep episode. Exploiting the temporal equivalence
between the daily quotient of scotophasic extension in autumn
and the running to completion of AG, the seasonal organism
deploys a largely astrocyte-based interval timer which renders
the generation of glycolytic products contingent upon a particular
photoperiod. On the diurnal time scale, export of products of
AG is viewed as taking place during the same REM sleep
episode proposed for the animal’s interrogation of crepuscular
lumiance. To be sure, the resulting conception of AG as
transpiring in sleep within selected astrocytic microdomains puts
us at odds with one aspect of the lymphatic system concept
as currently elaborated. For the latter positions AG strictly as
a waking-phase and cortical cascade driven by LC-grounded
(not medullary) NE (196). However in many other respects we
may involve the ready dietary availability of simple sugars. Casual and steady
consumption of exogenous sugars would likely overwhelm the photoperiodic
mechanism, one based primarily on a jealously guarded astrocytic storehouse of
the glucose polymer glycogen.
remain indebted to the glymphatic hypothesis. By incorporating a second noradrenergic focus involving the medullary system, the glymphatic metacooncept can be largely reconciled with the present model.

The third fundamental difference involves a significant revision of the anatomic substrate of mammalian seasonality. The aBNST is brought forward as an integral component of the seasonal network, one which communicates closely with previously documented nodes both by hard-wired pathways and through volume transmission taking place primarily in sleep. Aligned in multiple ways, both moieties of the aBNST (medial and lateral) together carry out a behavioral switch process permitting the organism to survive winter.

**What Does the Model Omit?**

Our hypothesis, the main features of which are listed in Box 3, can be taxed with any number of omissions. Hardly given their due, or even mentioned at all, are many likely actors in the photoperiodic process (some of which, intriguingly, do figure in recent work on the BNST). This includes pituitary due, or even mentioned at all, are many likely actors in the photoperiodic process (some of which, intriguingly, do figure in recent work on the BNST). This includes pituitary factors/PI3K signal cascades, and no doubt others. But if the model can serve heuristically to guide further research into the means whereby the photoperiodic mammal develops its remarkable response to seasonal change as well as into the manner in which human beings both inherited and mitigated this response, then the effort will have been worthwhile.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in this study are included within the article, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

The author confirms being the sole contributor of this work and has approved it for publication.

**ACKNOWLEDGMENTS**

I wish to express my gratitude to three reviewers for *Frontiers in Psychiatry* for incisive and cogent criticisms that led to significant improvements in the paper. I am also grateful to Sarah Joy Zimmerman of Joy Medical Illustration for help with the figures.

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