Running title: Neural programming of seasonality

Title: Neural programming of seasonal biology in birds and mammals: a modular perspective.

Authors: Tyler J Stevenson*, Timothy A Liddle, Calum Stewart, Christopher J Marshall, Gaurav Majumdar.

Affiliation: Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow G61 1QH, United Kingdom.

* Corresponding author:
Tyler Stevenson
235 Jarrett Building
Garscube Campus
Inst. Biodiversity, Animal Health and Comparative Medicine
University of Glasgow
Glasgow, G61 1QH
e. tyler.stevenson@glasgow.ac.uk

Disclosure statement: The authors have nothing to disclose.

Total words:
No Figures: 3

Key words: hypothalamus, thalamus, midbrain, reproduction, energy balance,

Abstract (250)

Most animals in the temperate zone exhibit robust seasonal rhythms in physiology and behavior. The integration of predictive and supplementary environmental cues (e.g., nutrients) involves a series of discrete, and interconnected brain regions that span hypothalamic, thalamic, mesencephalic, and limbic regions. These adaptive changes in neuroendocrine structures and cellular plasticity have likely evolved to support species-specific seasonal life-history transitions. Despite significant advances in our understanding of ecological responses to different environmental cues, there remains a paucity in literature on how these diverse cues impact the underlying neural and cellular substrates. To date, the predominant scientific approach has focussed on neuroendocrine responses to annual changes in daylength, referred to as photoperiod, due to the robust physiological changes to light manipulations in laboratory settings. Here, we highlight the relatively few animal models that have been effectively used to investigate how predictive day lengths, and supplementary cues are integrated across hypothalamic nuclei, and discuss the key findings of how seasonal rhythms in physiology are governed by adaptive neuroendocrine changes. We discuss how specific brain regions integrate environmental cues to form a multiple modal system that have evolved in to optimize timing of seasonal physiology. Overall, the review aims to highlight the existence of a modular network for the control of seasonal rhythms and indicates that natural selection can operate independently on different neuroanatomical and cellular substrates to support an organism's fitness.

Introduction

Most long-lived (i.e., >1yr) animals that inhabit temperate zones evolved neural mechanisms to time seasonal transitions in life-history traits (Wingfield et al., 1992, Ball, 1993, Stevenson et al., 2017). In some cases, there are simple stimulus-response events in which environmental cues, such as precipitation or social context, induce a seasonally adaptive specialized change in physiological stability (Hahn and MacDougall-Shackleton, 2008). There are also endogenous annual programs that anticipate the future and function to prepare an individual for predictable environmental change (Lincoln, 2019). These endogenous programmed changes in seasonal physiology are termed circannual rhythms, as the physiological oscillations will continue in the absence of any change in the environment (Helm and Stevenson, 2015). In this review, we will first discuss the current understanding of circannual rhythmicity in the central nervous system. Then, we will cover how different environmental cues are integrated across hypothalamic, limbic, and cortical brain regions, functioning to fine-tune the timing of seasonal physiology. An exhaustive overview of the neural response across all birds and mammals is beyond the scope of this review but instead, the paper will focus on a few select animal models. A comparative approach that draws from mouse and rat literature will be employed to propose a multi-modal neural system for the control of seasonal rhythms with examples focusing on sex-dependent and -independent control of reproductive physiology.

Programming seasonal physiology

Some of the best examples of endogenous seasonal rhythmicity in life history traits are observed in temperature birds (Wingfield et al., 2008). Studies in African stonechats (*Saxicola torquatus*) held in constant photoperiod and temperature conditions maintain oscillations in gonadal size and molt for up to 7.5 years (Gwinner and Dittami, 1990). The

period length of the oscillation averaged 9.1 +/- 1.9 months for the duration of the study resulting in nine complete cycles. Female stonechats exhibit an initial short period (i.e., 9-10 months) for the first three years and then subsequently lengthened annual rhythmicity to nearly 12 months thereafter. Endogenous circannual rhythms in migration and reproduction have been identified across a wide range of bird species and include Siberian stonechats (*Saxicola maurus*) (Helm et al., 2009), Pied flycatchers (*Ficedula hypoleuca*) (Helm et al., 2019), and Spotted munia (*Lonchura punctulata*) (Budki et al., 2012). The Golden-mantled ground squirrel (*Citellus lateralis*) is one of the most studied animal model and is particularly appropriate for the study of mammalian circannual programs. Under constant laboratory conditions of 12L:12D photoperiod and approximately 2ºC temperature, ground squirrels displayed annual cycles of hibernation and active phases consistent with wild conspecifics (Pengelley and Fisher, 1957). The precise neurobiological basis of circannual timing remains elusive, although the pars tuberalis of the anterior pituitary gland (Lincoln and Hazlerigg, 2010) and tanycytes (Lewis and Ebling, 2017) along the third ventricle of the hypothalamus have been proposed as potential substrates.

The annual change in daylength is a predictive environmental cue that is used by many birds (Dawson et al., 2001) and mammals (Goldman, 2001) to entrain endogenous programs in seasonal rhythms. The neurobiology of photoperiodism, or the neural coding of day length, is the best understood exogenous cue due to the robust changes in physiology (Farner and Follett, 1966; Hazlerigg and Wagner, 2006). Other environmental stimuli, such as social cues, temperature, and nutrient availability have been shown to influence sex-dependent seasonal reproduction to local environmental conditions (Ball and Ketterson, 2008, Tolla and Stevenson, 2020). Over the past couple decades, the use of immediate early gene expression in midbrain, hypothalamic, limbic, and cortical brain regions have shown a network of cellular activity that reflects the neural coding of social behavior in birds, mammals, and even

fish (Newman, 1999; Goodson, 2005). The patterns of immediate early gene activation and distribution of neuropeptides (e.g., vasotocin/vasopressin) provides insights on how seasonal social behaviour including aggression, affiliation, copulatory and parental behaviour are regulated (Goodson, 2005). Social behaviour has also been shown to effect gene expression related to seasonal reproduction in starlings (Perfito et al., 2015). Annual changes in temperature have long been known to impact timing of reproduction in birds (Visser, 2008) and emergence of hibernation in mammals (Inouye et al., 2000). External and visceral temperatures are detected and communicated to discrete neurons in the anterior hypothalamus/preoptic area (AH-POA) that integrate both warm- and cold-temperatures (Tan and McKnight, 2018). How these cells integrate local and transitive temperatures (e.g., vernal, autumnal) is not fully understood. This paper will discuss the neural integration of predictive and supplementary environmental cues and present a modular network for the timing of seasonal physiology.

Mammalian and Avian Animal Models for Mechanisms of Seasonal Rhythms

There was an exponential increase in the number of yearly publications on seasonality in mammals and birds from the 1970s to early 2000s (Fig.1A). The ecological perspective applied to seasonal rhythms in Great tit (*Parus major*) and Blue tit (*Cyanistes caeruleus*) (Visser et al., 2010) populations, along with Golden-mantled ground squirrel (Mrosovsky, 1975) and Red deer (*Cervus elaphus*) (Guinness et al., 1971), have been invaluable for interpretating how environmental cues are integrated at morphological and physiological levels. For many reasons, our understanding of the neural mechanisms that control seasonal rhythms have relied on relatively few animal models that adapted well to laboratory conditions. Animal models used for most laboratory-controlled experiments include biomedical mice, rats, sheep, hamsters, and chickens (Fig.1B). Studies of seasonal rhythms in

sheep have largely focused on veterinary medicine (Scheerlinck et al., 2008) and basic science (Lehman et al., 2002). The large hypothalamic and pituitary tissue obtained from sheep presents as a valuable system to uncover the role of reproductive neuropeptides (Weems et al., 2015) and photoperiodic (Lincoln et al., 2003) control of seasonal rhythms. White-footed mice (*Peromyscus leucopus*) has been used as a model organism for the study of mammalian seasonality for decades and is currently the second most common model documented within publications referencing seasonality (Fig.1B). In wild and laboratory conditions, white-footed mice exhibit reliable, and predictable physiological responses to changing light conditions. They also exhibit a short-term form of hibernation referred to as torpor, in response to decreasing day lengths (Lynch et al, 1978). A significant advantage of using white-footed mice has been the availability of a quality genome since 2002 (Waterston and Pachter, 2002), that has facilitated gene-behavior relationship analyses. Siberian hamster (*Phodopus Sungorus*) with its recently available genome sequence (Bao et al., 2019) has also been a useful model due to the small size, robust physiological rhythms in response to photoperiodic changes facilitating large scale studies. In Siberian hamsters, short photoperiods drive significant decreases in body mass, which lead to a large drop in energy requirements for thermoregulation to survive winter conditions (Heldmaier and Steinlechner, 1981). They lose body mass through a period of food restriction which recovers to a seasonally appropriate mass after food availability which reflects programmed circannual processes (Ebling and Barrett, 2008). Siberian hamsters are also seasonal breeders, having offspring in summer when resources are abundant. To facilitate this, short days drive significant gonadal regression and subsequent recrudescence in both males and females (Gorman and Zucker, 1995).

In birds, Japanese quail (*Coturnix japonica*) is widely regarded as a model species for the study of avian seasonal reproduction in a laboratory setting (Huss et al, 2008). Benefits of

151 selecting quail are high rate of maturation (approximately 6 weeks) and fast growth rate
152 (Boon et al, 2000). Furthermore, the Japanese quail shows an extremely robust photoperiodic
153 response including testes mass, with some reports suggesting an approximately 200-250-fold
154 increase following the onset of reproductive investment (Sachs, 1967; Yasuo et al, 2006).
155 Perhaps most crucially for the investigation of seasonal rhythms, the Japanese quail has a
156 rapid and robust neuroendocrine response to variable photoperiods (Yasuo et al, 2006).
157 Another avian model, red-headed buntings (*Emberiza bruniceps*), exhibit robust shifts in
158 locomotor behaviour that accurately mimics a major life history transition: migration. Short,
159 winter-like photoperiods maintain a non-migratory state and the switch to long summer-like
160 photoperiods induces pre-migratory fattening followed by nocturnal migratory behavior (i.e.
161 zugunruhe) (Kumar et al. 2010; Stevenson and Kumar, 2017). An important adaptation for
162 seasonal migration is weight gain and fat storage, which is visible in the sub-cutaneous fat
163 stores. This weight gain is induced by hyperphagia (Bairlein, 1985) and/or a diet-selection
164 shift in response to changes in the environmental photoperiod (Bairlein, 1998). The bunting
165 model provides a unique system where seasonal rhythms of the metabolic regulation at
166 behavioral, physiological, neuroanatomical, or molecular level can be studied.
167

168 **Modular basis for the neuroendocrine control of seasonal physiology**

169 The neural integration of environmental and endogenous programs is limited to a few discrete
170 regions (Ball, 1993). Some brain regions have functional connections with seasonal programs
171 in physiology, such as the AH-POA control of body temperature (Satinoff E et al., 1976) and
172 sex-specific reproductive behavior (Nance et al., 1977) (Fig.2). Although the control of
173 feeding behavior is primarily driven by the arcuate nucleus in the hypothalamus, other neural
174 substrates such as the ventromedial nucleus, lateral hypothalamus and mesencephalic regions
175 contribute to long-term changes in body mass and metabolism (Elmquist et al., 1999) (Fig.2).

Here, we will cover the neural structures and cellular components that underlie how hypothalamic and extra-hypothalamic regions form modular networks for the control of seasonal rhythms. Using commonalities across mammalian and birds models described above, the perspective that evolutionary pressures can shape independent variation in the neural modular control of seasonal physiology and establish the range of different morphological and phenotypic variation will be presented.

Modular control of seasonal physiology in birds

Anterior hypothalamus-preoptic area, mediobasal-hypothalamus, and the photoperiodic response

Research on seasonal biology in birds has focused mostly on the photoperiod based neural control of reproduction. Of this, Gonadotropin releasing hormone (GnRH) which is a highly conserved neuropeptide required for sexual reproduction in all amniotes (Fernald and White, 1999) has been a focus for a bulk of studies. GnRH neurons are localized to the AH-POA and control seasonal rhythms in bird and mammalian reproduction (Stevenson et al., 2012a). Both environmental and endogenous programs in the control of seasonal rhythms must act either at the level of the neuronal GnRH cell, release of GnRH into the pituitary gland, or the receptor of GnRH cells on gonadotropes in the anterior pituitary gland. Annual changes in photoperiodic control of GnRH synthesis have evolved to facilitate different degrees of adaptive flexibility in seasonal timing (MacDougall-Shackleton et al., 2009). Photoperiod also regulates the release of GnRH from the median eminence into the anterior pituitary gland by a local circuit that involves pars tuberalis thyrotropin-stimulating hormone-β signalling to 3rd ventricle ependymal cells (Nakao et al., 2008) to control tanycytes retraction (Yamamura et al., 2004) that functions to block or permit neuropeptide communication. The current proposition is that annual changes in photoperiod provides dual neuroendocrine control over

seasonal rhythms in reproduction, by acting at the level of GnRH synthesis in the AH-POA and GnRH release into the median eminence (Dawson et al., 2001; Stevenson et al., 2012b). Integration of photoperiodic cues by the GnRH system is dependent on light detection by photoreceptor(s) localized in the hypothalamus. Across avian taxa, multiple light responsive opsin photoreceptors are known to be present in hypothalamus like rhodopsin, melanopsin, neuropsin, VA opsin etc with recent evidence suggesting vertebrate ancient opsin (VA opsin) and neuropsin (Opn5) to be the leading candidates for deep brain photoreception (Pérez et al., 2019). VA opsin neurons co-localize with GnRH neurons and may directly regulate expression levels (Pérez et al., 2022).

Distributed neural network integrates social cues

Social cues modulate GnRH synthesis and release in birds. In European starlings (*Sturnus vulgaris*), males that are housed with a female had significantly more GnRH-expressing neurons compared to singly housed birds and suggest that visual, auditory, or tactile stimuli from a female enhanced neuroendocrine regulation of reproduction (Stevenson and Ball, 2009). Social cues also impact GnRH release by affecting the ependymal layer expression Deiodinase type-2 (*Dio2*) enzyme. The presence of a potential male mate significantly increased *Dio2* expression in female starlings which was positively associated with increased follicle volume, a direct consequence of elevated gonadotropin secretion (Perfito et al., 2015). The discovery of Gonadotropin-inhibitory hormone (GnIH) opened an entirely new avenue of research into how supplementary cues impact reproduction (Tsutsui et al., 2021). GnIH is primary localized to the paraventricular nucleus in the hypothalamus and directly inhibits GnRH release (Bentley et al., 2003). *GnIH* expression reflects the social environment as paired starlings have reduced levels in the hypothalamus and resulted in the facilitation of gonadotropin release (Calisi et al., 2011). Integration of social cues by AH-POA GnRH, and

PVN GnIH expressing cells must include visual, auditory, and tactile cues that are distributed across neural networks. A 'social behavior network' consisting of highly interconnected limbic and cortical brain regions in mammals (Newman, 1999) and has been adapted to birds (Goodson, 2005). This social behavior network contains multiple neuropeptides such as vasotocin and oxytocin that guide seasonal changes in affiliation, aggression, and sociality (e.g., gregarious) (Goodson et al., 2005). These findings illustrate the multiple hypothalamic and extra-hypothalamic neural structures and specific cellular populations converge on GnRH to regulate seasonal timing in reproduction.

Dorsomedial- and mediobasal-hypothalamus and the control of energy stability

While behavioural, physiological, and molecular studies have been done on several species of migratory birds and animals as such, few studies have been done on the neurobiological or anatomical corelates of metabolism associated with migration. Recent research in red headed bunting suggested that the dorsomedial hypothalamus (DMH) and median eminence (ME) may serve as crucial neurobiological substrates for the metabolic needs associated with migration (Majumdar et al., 2021). Clever comparisons of neurogenesis and expression of neuropeptide Y (NPY) between a non-migratory seasonal bird which shows no weight gain in response to changing daylengths and migratory buntings provided for the first evidence that MBH in birds also serves as neurogenic niche as demonstrated in mammals (Lee et al., 2010). One hypothesis is that this neurogenic niche is involved in diet related weight gain (Lee et al., 2012). Presence of strong correlations of body mass gain with hypothalamic neurogenesis in response to high calorie diet and photoperiod otherwise absent in the non-migratory birds

hints that hypothalamic neurogenesis may be a regulator of weight gain and metabolism across species (Majumdar et al., 2021).

Buntings undergo two migrations, spring migration towards breeding grounds and autumn migration towards overwintering grounds. Transcriptome profiling of hypothalamic and liver tissues of spring migrants revealed an interesting upregulation of calcium binding gene, ATP2A suggesting that increased calcium uptake is involved in energy stability (Sharma et al., 2018). ATP2A gene is responsible for the increased transport of fat from the liver and thus can aid in minimizing the risk of developing of metabolic syndrome like fatty liver disease. A similar upregulation of genes associated with myelin sheath and focal adhesion were found in MBH (Sharma et al., 2018). The spring and autumn migration shows contrasting physiological characteristics with a seasonal metabolic plasticity, particularly in the accumulation, mobilization, and utilization of fat. Consistent with previous results, seasonal life history events such as migration depend on pyruvate decarboxylase along with malate dehydrogenase gene was found indicating a requirement of acetyl-CoA to support migratory behavior (Majumdar et al., 2021). Not surprisingly mRNA levels of fatty-acid synthase were also found along with differences in adipose triglyceride lipase and lipoprotein lipase suggest that triglycerides and/or free fatty acids are the main metabolic substrates for spring migration (Sharma and Kumar, 2019, Majumdar et al., 2021). A contrast of expression between spring and autumn migration was also found in fatty acid binding protein and fatty acid translocases demonstrating a differential fat fuel supply (Sharma and Kumar 2019).

Seasonal transitions in life-history traits are often energetically demanding (Murphy and Ebling, 2011). Recent studies in Black- and Red-headed buntings has shown a significant shift of the MBH transcriptomic landscape (Trivedi et al., 2014, Majumdar et al., 2015, Sharma et al., 2019, Majumdar et al., 2021). While comparing the seasonal non-migratory with the migratory states in migratory black-headed buntings where bunting display a

significant weight gain, fatty-acid synthase was expressed at higher levels in the hypothalamus during premigratory and migratory stages. Trivedi and colleagues (2014) argue an increased lipogenic activity during photostimulated premigratory and migratory states is required to ensure sufficient energy stores are available. In comparison, genes involved in glucose metabolism were less effected by seasonal migratory life history transitions. In Red headed buntings which were exposed to one single long photoperiod of different lengths, only succinate dehydrogenase and malate dehydrogenase showed a daylength-dependent change in MBH expression (Majumdar et al., 2015). This may mean that although molecular regulation of metabolism parallels the physiology, light may also influence metabolism directly by acting on hypothalamic substrates.

Modular basis of the neural control of seasonal rhythms in mammals

Distributed network for photoperiodic control of seasonal physiology

Nocturnal duration of melatonin is the primary mechanism in which day lengths are encoded in the mammalian brain (Goldman, 2001). Melatonin binds to melatonin receptor 1c subtype to drive seasonal programs in physiology (Prendergast, 2010). The action of melatonin is widely distributed in the mammalian brain with most species having expression in the suprachiasmatic nuclei, median eminence/pars tuberalis, dorsomedial nucleus of the hypothalamus, and multiple thalamic and mesencephalic regions (Weaver et al., 1989). Similar to birds, thyrotropin-stimulating hormone-β expression is a cellular correlate of daylength and guides seasonally appropriate morphological changes in tanycytes along the 3rd ventricle (Hanon et al., 2008). In long-day breeding rodents, the short-day induced tanycytes deiodinase type-3 expression is the earliest identified molecular change, and the long-term exposure to constant winter-like daylengths results in inhibition in levels (Stevenson and Prendergast, 2013). The photoperiodic regulation of tanycytes extension and retraction is

likely a conserved mechanism in amniotes to control GnRH release. Unlike birds, GnRH synthesis remains relatively constant across seasonal states in rodents (Bernard et al., 1999). Instead, multiple neurotransmitters including dopamine, serotonin, glutamate, gamma-aminobutyric acid, and neuropeptides (e.g., kisspeptin, RF-amide related peptide-3) function to regulate GnRH activity (Malpaux et al., 1999). Since the discovery of kisspeptin (Seminara et al., 2003), several laboratories such as Gregory Demas (Greives et al., 2006) and Valerie Simonneaux (Saenz de Miera et al., 2014) groups have shown that expression in the anteroventral periventricular nucleus is positively related to reproductive state, and that injections elevate gonadotropin release. These data indicate that a conserved AH-POA and median eminence pathway for the neuroendocrine control of GnRH activity and release is function similarly in birds and mammals. The divergence and diversification of birds over 150 million years ago (Brusatte et al., 2015) likely resulted in the loss of kisspeptin signalling and modulatory inputs from anteroventral periventricular hypothalamic cellular populations. How and where other neuromodulatory inputs such as dopamine, integrate melatonin signalling of day length is poorly understood.

Arcuate nucleus controls programmed changes in energy stability

Arcuate, ventromedial, and lateral hypothalamic nuclei are well established brain regions for the control of feeding and energy stability (Elmquist et al., 1999). The neuropeptide, proopiomelanocortin (POMC) is an evolutionary conserved pleiotropic gene that exhibits large scale seasonal changes in expression (Helfer and Stevenson, 2020). Across mammalian species, increased body mass, one parameter of energy balance, is positively associated with arcuate *Pomc* expression in hamsters (Bao et al., 2019), rats (Ross et al., 2015) and sheep (Archer et al., 2004). Recent work has identified that VGF nerve growth factor (VGF) is expressed in tanycytes and infusions of one derivative, TLQP-21 reduced body weight and

323 food intake (Lewis et al., 2017; Lisci et al., 2019). Both *Pomc* and *VGF* are expressed at high
324 levels in long photoperiod Siberian hamsters compared to short photoperiod housed animals
325 (Bao et al., 2019; Barrett et al., 2005). Indeed, a complex relationship between neural and
326 peripheral systems functions to maintain programmed seasonal changes in energy balance
327 and photoperiodic switches in these two neuropeptides likely integrate both circulating
328 hormonal signals of satiety and hunger, with the anticipation of future summer, or winter
329 conditions (Stevenson and Helfer, 2019).

330 Undoubtedly, neural modules that govern the integration of environmental cues
331 interact to coordinate seasonal physiological responses. The integration of supplementary
332 environmental cues by the master molecular of reproduction, GnRH, is one good example
333 (Fig.3). First order neurons in the circuits driving hunger and feeding behaviour are well
334 positioned to relay energy status to the GnRH neural network, suppressing fertility when food
335 sources are scarce, and the organism falls into negative energy status. These neurons express
336 the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) (Hahn et al.,
337 1998), and rodent studies have shown that virtually all AgRP neurons are GABAergic
338 (Horvath et al., 1997; Marshall et al., 2017). Direct AgRP neuron signalling on GnRH
339 neurons are well established. Evidence from light and electron microscopy provide extensive
340 morphologic evidence of synapses between AgRP neuron terminals and the proximal regions
341 of GnRH neurons, including in humans (Campbell et al., 2001). Electron microscopy further
342 reveals these synapses are symmetric in nature (Tsuruo et al., 1990; Turi et al., 2003). The
343 observed effects of NPY neuron signalling on GnRH neurons suggest a predominantly
344 inhibitory role. Applying NPY receptor agonists to GnRH neurons show that they are largely
345 inhibited by activation of the NPY Y1 receptor (Roa and Herbison, 2012), while a small
346 subset of neurons was excited by agonists for the Y4 receptor. Additionally, there is evidence
347 in GnRH neurons from nasal explants that suggests Y1 receptor activation inhibits GnRH

neurons by activating G protein-coupled inwardly rectifying potassium channels (Klenke et al., 2010). For example, 70% of GnRH neurons are excited by Pomc derived alpha-melanocortin stimulating hormone (MSH) acting on melatocortin-3 (MC3R) and -4 receptor (MC4R) and induce, an excitatory affect (Roa and Herbison, 2012). Immunohistochemical studies demonstrate terminals that are immunoreactive for adrenocorticotropic hormone (ACTH) (Leranth et al. 1988) and beta-endorphin (Chen et al. 1989), both cleavage products of *Pomc*, synapse with GnRH neuron cell bodies. There are fewer functional studies but MC3R and MC4R knockout leads to a decrease in litter size (Begriche et al. 2011) and fewer ovarian corpora lutea suggesting less frequent ovulation in females (Sandrock et al. 2009), indicating a direct negative effect on fecundity. Altogether, these data suggest that *Pomc* may play a supplemental but not necessary role in stimulating GnRH neurons, but more research is necessary to define their exact role.

Another way in which GnRH neuron activity can be assayed is by measuring changes in circulating luteinizing hormone (LH) release, as LH pulses are invariably preceded and driven by pulsatile GnRH release (Clarke and Cummins, 1982; Levine et al., 1982; Moenter et al., 1992). Of the substrates expressed by AgRP neurons, the most evidence for modulation of LH release comes from examining the effect of NPY. NPY administration in rodents often stimulates LH secretion (Bauer-Dantoin et al., 1991). This perhaps stems from NPY acting directly upon gonadotrophs, as NPY signalling and Y1 receptor activation potentiates LH release in response to GnRH signalling (Hill et al., 2004). It should also be noted that AgRP neurons may suppress GnRH neurons indirectly by inhibiting excitatory afferents (Padilla et al., 2017), thus possessing multiply levels at which AgRP neurons can modulate GnRH neuron activity and LH release.

Future directions

373 This review has predominantly focused on the role of neural modules involved in
374 reproduction and energy balance, and how the function of a few neuropeptides governs
375 seasonal physiology, respectively. The conjecture proposed was discrete neural substrates
376 control key physiological processes and that each module (e.g., AH-POA, Arcuate) has
377 autonomous functionality. The independent neuropeptidergic activity is a mechanism for
378 evolutionary pressures to act to shape how an organism times physiological, and behavioral
379 traits to environmental cues. Most research has used non-traditional animal models that have
380 lacked genomic information, and the ability to shape gene-environment studies. The past
381 decade has observed an explosion in the ability to sequence nucleic acids with whole
382 genomes, epigenomes, transcriptomes, and proteomes sequenced rapidly and at ever
383 increasing affordability. These high-throughput analyses are essential to uncover the entire
384 complement of genomic plasticity, and neuroanatomical specificity of seasonal control of
385 physiology. Research is currently stymied due to two relatively complex issues: genome
386 modifications and mathematical modelling. Current approaches to manipulate genome
387 function rely on short-hairpin RNA that are packaged into viral vectors. Although this
388 strategy is useful for short-term disruption in transcript levels, it is limited in the ability to
389 assess long-term inhibition of target genes. The development of cluster regularly interspaced
390 short palindromic repeats (CRISPR) and related associated protein-9 (Cas9) has ushered in a
391 new era in which select targets can be over-expressed, and mutated, to facilitate analyses of
392 genome function, and neuroanatomical specificity required for seasonal studies. Some
393 progress has already been achieved in non-traditional animal models such as Japanese quail
394 (Lee et al, 2019). Lastly, the large sequencing databases available, and soon, will reveal a
395 new challenge for seasonal biologists, the abundance of potential genes/transcripts/proteins
396 across different neural substrates, and understanding how the timing of each level is
397 coordinated across neural networks. Here, mathematical modelling using artificial

intelligence will be essential to handle the mass amounts of data in a logical, and meaningful way. Early work using an information theory approach with contingency-constancy modelling to both ecological (Wingfield et al., 1992) and neuroendocrine (Stevenson and Ball, 2011) levels of analyses provide a strong foundation to build complex models that can incorporate the wide range of brain regions and cellular processes that control seasonal physiology.

Acknowledgements:

This work was funded by a Leverhulme Trust Research Leader award to TJS. Figure 3 was created using Biorender.com.

409 **References:**

410 Archer, Z.A., Findley, P.A., McMillen, S.R., Rhind, S.M., Adam, C.L., 2015. Effects of
411 nutritional status and gonadal steroids on expression of appetite-regulatory genes in the
412 hypothalamic arcuate nucleus of sheep. J. Endocrinol. 182, 409-419.
413 Bairlein, F., 1985. Body weights and fat deposition of Palaearctic passerine migrants in the
414 central Sahara. Oecologia 66, 141-146.
415 Bairlein, F., 1998. The effect of diet composition on migratory fuelling in Garden Warblers
416 Sylvia borin. J. Avian Biol. 29, 546-551.
417 Ball, G.F., Ketterson, E.D., 2008. Sex differences in the response to environmental cues
418 regulating seasonal reproduction in birds. Philos. Trans. R. Soc. Lond. B. Biol. Sci.
419 363, 231-246.
420 Bao, R., Onishi, K.G., Tolla, E., Ebling, F.J., Lewis, L.E., Anderson, R.L., Barrett, P.,
421 Prendergast, B.J., Stevenson, T.J., 2019. Genome sequencing and transcriptome
422 analyses of the Siberian hamster hypothalamus identify mechanisms for seasonal
423 energy balance. Proc. Natl. Acad. Sci. 116, 13116-13121.
424 Barrett, P., Ross, A.W., Balik, A., Littlewood, P.A., Mercer, J.G., Moar, K.M., 2005.
425 Photoperiodic regulation of histamine H3 receptor and VGF messenger ribonucleic acid
426 in the arcuate nucleus of the Siberian hamster. Endocrinol. 146, 1930-1939.
427 Bauer-Dantoin, A.C., McDonald, J.K., Levine, J.E., 1991.Neuropeptide Y potentiates
428 luteinizing hormone (LH)-releasing hormone-stimulated LH surges in pentobarbital-
429 blocked proestrous rats. Endocrinol. 129, 402-8.
430 Begriche, K., Levasseur, P.R., Zhang, J., Rossi, J., Skorupa, D., Solt, L.A., Young, B., Burris,
431 T.P., Marks, D.L., Mynatt, R.L., Butler, A.A., 2011. Genetic dissection of the functions
432 of the melanocortin-3 receptor, a seven-transmembrane G-protein-coupled receptor,

433 suggests roles for central and peripheral receptor in energy homeostasis. J. Biol. Chem.
434 286, 40771-40781.
435 Bentley, G.E., Perfito, N., Ukena, K., Tsutsui, K., Wingfield, J.C., 2003. Gonadotropin-
436 inhibiting peptide in song sparrows (Melospiza melodia) in different reproductive
437 conditions, and in house sparrows (Passer domesticus) relative to chicken
438 gonadotropin-releasing hormone. J. Neuroendocrinol. 15, 794-802.
439 Bernard, D.J., Abuav-Nussbaum, R., Horton, T.H., Turek, F.W., 1999. Photoperiodic effects
440 on gonadotropin-releasing hormone (GnRH) content and the GnRH-immunoreactive
441 neuronal system of male Siberian hamsters. Biol. Reprod. 60, 272-276.
442 Boon, P., Visser, G.H., Daan, S., 2000. Effect of photoperiod on body weight gain, and daily
443 energy intake and energy expenditure in Japanese quail (Coturnix c. Japonica). Physiol.
444 Behav. 70, 249-260.
445 Brusatte, S.L., O'Connor, J.K., Jarvis, E.D., 2015. The origin and diversification of bords.
446 Curr. Biol. 25, R888-R898.
447 Budki, P., Rani, S., Kumar, V., 2012. Persistence of circannual rhythms under constant
448 periodic and aperiodic light conditions: sex differences and relationship with the
449 external environment. J. Exp. Biol. 215, 3774-3785.
450 Calisi, R.M., Diaz-Munoz, S.L., Wingfield, J.C., Bentley, G.E., 2011. Social and breeding
451 status are associated with the expression of GnIH. Genes Brain Behav. 10, 557-564.
452 Campbell, R.E., Ffrench-Mullen, J.M.H., Cowley, M.A., Smith, M.S., Grove, K.L., 2001.
453 Hypothalamic circuitry of neuropeptide Y regulation of neuroendocrine function and
454 food intake via the Y5 receptor subtype. Neuroendocrinol. 74, 106-19.
455 Chen, W.P., Witkin, J.W., Silverman, A.J., 1989. Beta-Endorphin and gonadotropin-releasing
456 hormone synaptic input to gonadotropin-releasing hormone neurosecretory cells in the
457 male rat. J. Comp. Neurol. 286, 85-95.

458 Clarke, I.J., Cummins, J.T., 1982. The temporal relationship between gonadotropin releasing
459 hormone (GnRH) and luteinizing hormone (LH) secretion in ovariectomized ewes.
460 Endocrinol. 111, 1737-9.
461 Dawson, A., King, V.M., Bentley, G.E., Ball, G.F., 2001. Photoperiodic control of
462 seasonality in birds. J. Biol. Rhythm 16, 365-380.
463 Ebling, F., Barrett, P., 2008. The regulation of seasonal changes in food intake and body
464 weight. J. Neuroendocrinol. 20, 827–833.
465 Elmquist, J.K., Elias, C.F., Saper, C.B., 1999. From lesions to leptin: hypothalamic control of
466 food intake and body weight. Neuron, 22, 221-232.
467 Farner, D.S., Follett, B.K., 1966. Light and other environmental factors affecting avian
468 reproduction. J. Anim. Sci. 26, 90-118.
469 Fernald, R.D., White, R.B., 1999. Gonadotropin-releasing hormone genes: phylogeny,
470 structure and functions. Front. Neuroendocrinol. 20, 224-240.
471 Goldman, B.D., 2001. Mammalian photoperiodic system: formal properties and
472 neuroendocrine mechanisms of photoperiodic time measurement. J. Biol. Rhythms, 16,
473 283-301
474 Goodson, J.L., 2005. The vertebrate social behavior network: evolutionary themes and
475 variations. Horm. Behav. 48, 11-22.
476 Goodson, J.L., Evans, A.K., Lindberg, L., Allen, C.D., 2005. Neuro-evolutionary patterning
477 of sociality. Proc. Biol. Sci. 272, 227-235.
478 Gorman, M.R., Zucker, I., 1995. Testicular regression and recrudescence without subsequent
479 photorefractoriness in Siberian hamsters. Amer. J. Physiol. Reg. Intgr. Comp. Physiol.
480 269, R800–R806.

481 Greives, T.J., Mason, A.O., Scotti, M.A.L., Levine, J., Ketterson, E.D., Kriegsfeld, L.J.,
482 Demas, G.E., 2007. Environmental control of kisspeptin: implications for seasonal
483 reproduction. Endocrinol. 148, 1158-1166.
484 Guinness, F., Lincoln, G.A., Short, R.V., 1971. The reproductive cycle of the female red
485 deer, Cervus elaphus. J. Reprod. Fertil. 27, 427-438.
486 Gwinner, E., Dittami, J., 1990. Endogenous reproductive rhythms in a tropical bird. Science
487 249, 906-908.
488 Hahn, T.P., MacDougall-Shackleton, S.A., 2008. Adaptive specialization, conditional
489 plasticity and phylogenetic history in the reproductive cue response system of birds.
490 Philos. Trans. R. Soc. B. Biol. 363, 267-286.
491 Hahn, T.M., Breininger, J.F., Baskin, D.G., Schwartz, M.W., 1998. Coexpression of Agrp
492 and NPY in fasting-activated hypothalamic neurons. Nature Neurosci 1, 271-272.
493 Hanon, E.A., Lincoln, G.A., Fustin, J.M., Dardente, H., Masson-Pevet, M., Morgan, P.J.,
494 Hazlerigg, D.G., 2008. Ancestral TSH mechanism signals summer in a photoperiodic
495 mammal. Curr. Biol. 18, 1147-1152.
496 Hazlerigg, D.G., Wagner, G.C., 2006. Seasonal photoperiodism in vertebrates: from
497 coincidence to amplitude. Trends Endocrinol. Metab. 17, 83-91.
498 Heldmaier, G., Steinlechner, S., 1981. Seasonal control of energy requirements for
499 thermoregulation in the Djungarian hamster (Phodopus sungorus), living in natural
500 photoperiod. J. Comp. Physiol. 142. 429–437.
501 Helfer, G., Stevenson, T.J., 2020. Pleiotropic effects of proopiomelanocortin and VGF nerve
502 growth factor inducible neuropeptides for the long-term regulation of energy balance.
503 Mol. Cell Endocrinol. 514, 110876.
504 Helm, B., Schwabl, I., Gwinner, E., 2009. Circannual basis of geographically distinct bird
505 schedules. J. Exp Biol. 212, 1259-1269.

506 Helm, B., Stevenson, T.J., 2015. Circannual rhythms: history, present challenges, future
507 directions. In Annual, lunar and tidal clocks: patterns and mechanisms of nature's
508 enigmatic rhythms. Numata, H & Helm B (eds) Springer Japan: Tokyo. Pg 213-225.
509 Helm, B., Van Doren, B.M., Hoffmann, D., Hoffmann, U.. 2019. Evolutionary response to
510 climate change in migratory Pied Flycatchers. Curr. Biol. 29, 3714-3719.
511 Hill, J.W., Urban, J.H, Xu, M., Levine, J.E., 2004. Estrogen Induces Neuropeptide Y (NPY)
512 Y1 Receptor Gene Expression and Responsiveness to NPY in Gonadotrope-Enriched
513 Pituitary Cell Cultures. Endocrinol. 145, 2283-2290.
514 Horvath, T.L., Bechmann, I., Naftolin, F., Lara, S.P., Leranth, A.B., 1997. Heterogeneity in
515 the neuropeptide Y-containing neurons of the rat arcuate nucleus: GABAergic and non-
516 GABAergic subpopulations. Brain Res. 756, 283-286.
517 Huss, D., Poynter, G., Lansford, R., 2008. Japanese quail (Coturnix japonica) as a laboratory
518 animal model. Lab Animal, 37, 513-519.
519 Inouye, D.W., Barr, B., Armitage, K.B., Inouye, B.D. 2000. Climate change is affecting
520 altitudinal migrants and hibernating species. Proc. Natl Acad. Sci. 97, 1630-1633.
521 Klenke, U., Constantin, S., Wray, S., 2010. Neuropeptide Y directly inhibits neuronal activity
522 in a subpopulation of gonadotropin-releasing hormone-1 neurons via Y1 receptors.
523 Endocrinol. 151, 2736-46.
524 Kumar, V., Wingfield, J.C., Dawson, A., Ramenofsky, M., Rani, S., Bartell, P., 2010.
525 Biological clocks and regulation of seasonal reproduction and migration in birds.
526 Physiol. Biochem. Zool. 83, 827-835.
527 Lee, J., Ma, J., Lee, K., 2019. Direct delivery of adenoviral CRISPR/Cas9 vector into the
528 blastoderm for generation of targeted gene knockout in quail. Proc. Natl. Acad. Sci.
529 116, 13288-13292.

530 Lee, D.A., Bedont, J.L., Pak, T., Wang, H., Song, J., Miranda-Angulo, A., Takiar, V.,
531 Charubhumi, V., Balordi, F., Takebayashi, H., Aja, S., Ford, E., Fishell, G., Blackshaw,
532 S., 2012. Tanycytes of the hypothalamic median eminence form a diet-responsive
533 neurogenic niche. Nat Neurosci. 15, 700-702.
534 Lehman, M.N., Coolen, L.M., Goodman, R.L., Viguie, C., Billings, H.J., Karsch, F.J., 2002.
535 Seasonal plasticity in the brain: the use of large animal models for neuroanatomical
536 research. Reprod Suppl. 59, 149-165.
537 Leranth, C., MacLusky, N.J., Shanabrough, M., Naftolin, F., 1988. Immunohistochemistal
538 evidence for synaptic connections between pro-opiomelanocortin-immunoreactive
539 axons and LH-RH neurons in the preoptic area of the rat. Brain Res. 449, 167-176.
540 Levine, J.E., Pau, K.Y., Ramirez, V.D., Jackson, G.L., 1982. Simultaneous measurement of
541 luteinizing hormone-releasing hormone and luteinizing hormone release in
542 unanesthetized, ovariectomized sheep. Endocrinol. 111, 1449-55.
543 Lewis, J.E., Brameld, J.M., Hill, P., Cocco, C., Noli, B., Ferri, G.L., Barrett, P., Ebling,
544 F.J.P., Jethwa, P.H., 2017. Hypothalamic over-expression of VGF in the Siberian
545 hamster increases energy expenditure and reduces body weight gain. PloS One 12,
546 e0172724.
547 Lewis, J.E., Ebling, F.J., 2017. Tanycytes as regulators of seasonal cycles in neuroendocrine
548 function. Front. Neurol. 8, 79.
549 Lincoln, G.A., 2019. A brief history of circannual time. J. Neuroendocrinol. 31, e12694.
550 Lincoln, G.A., Hazlerigg, D.G., 2010. Mammalian circannual pacemakers. Soc. Reprod.
551 Fertil. Suppl. 67, 171-186.
552 Lincoln, G.A., Andersson, H., Loudon, A., 2003. Clock genes in calendar cells as the basis of
553 annual timekeeping in mammals – a unifying hypothesis. J. Endocrinol. 179, 1-13.

554 Lisci, C., Lewis, J.E., Daniel, Z.C.T.R., Stevenson, T.J., Monnier, C., Marshall, H.J., Fowler,
555 M., Ebling, F.J.P., Ferri, G.L., Cocco, C., Jethwa, P.H., 2019. Photoperiodic changes in
556 adiposity increase sensitivity of female Siberian hamsters to systemic VGF derived
557 peptide TLQP-21. PloS One 14, e0221517.
558 Lynch, G.R., White, S.E., Grundel, R., Berger, M.S., 1978. Effects of photoperiod, melatonin
559 administration and thyroid block on spontaneous daily torpor and temperature
560 regulation in the white-footed mouse, Peromyscus leucopus. J. Comp. Physiol. 125, 57-
561 163.
562 Marshall, C.J., Desroziers, E., McLennan, T., Campbell, R.E., 2017. Defining
563 Subpopulations of Arcuate Nucleus GABA Neurons in Male, Female, and Prenatally
564 Androgenized Female Mice. Neuroendocrinol. 105, 157-169.
565 MacDougall-Shackleton, S.A., Stevenson, T.J., Watts, H.E., Pereyra, M.E., Hahn, T.P., 2009.
566 The evolution of photoperiod response systems and seasonal GnRH plasticity in birds.
567 Integr. Comp. Biol. 49, 580-589.
568 Majumdar, G., Rani, S., Kumar, V., 2015. Hypothalamic gene switches control transitions
569 between seasonal life history states in a night-migratory photoperiodic songbird. Mol.
570 Cell Endocrinol. 399, 110-21.
571 Majumdar, G., Yadav, G., Malik, S., Rani, S., Balthazart, J., Kumar, V.. 2021. Hypothalamic
572 plasticity in response to changes in photoperiod and food quality: An adaptation to
573 support pre-migratory fattening in songbirds? Eur. J. Neurosci. 53, 430-448.
574 Malpaux, B., Thiery, J.C., Chemineau, P., 1999. Melatonin and the seasonal control of
575 reproduction. Reprod. Nutr. Dev. 39, 355-366.
576 Moenter, S.M., Brand, R.M., Midgley, A.R., Karsch, F.J., 1990. Dynamics of gonadotropin-
577 releasing hormone release during a pulse. Endocrinol. 130, 503-10

578 Mrosovsky, N., 1975. The amplitude and period of circannual cycles of body weight in
579 golden-mantled ground squirrels with medial hypothalamic lesions. Bran Res. 99, 97-
580 116.
581 Murphy, M., Ebling, F.J.P., 2011. The role of hypothalamic tri-iodothyronine availability in
582 seasonal regulation of energy balance and body weight. J. Thyroid Res. 387562.
583 Nakao, N., Ono, H., Yamamura, T., Anraku, T., Takagi, T., Higashi, K., Yasuo, S., Katou,
584 Y., Kageyama, S., Uno, Y., Kasukawa, T., Iigo, M., Sharp, P.J., Iwasawa, A., Suzuki,
585 Y., Sugano, S., Niimi, T., Mizutani, M., Namikawa, T., Ebihara, S., Ueda, H.R.,
586 Yoshimura, T., 2008. Thyrotrophin in the pars tuberalis triggers photoperiod response.
587 Nature 452, 317-322.
588 Nance, D.M., Christensen, L.W., Shryne, J.E., Gorski, R.A., 1977. Modifications in
589 gonadotropin control and reproductive behavior in the female rat by hypothalamic and
590 preoptic lesions. Brain Res. Bull. 4, 307-312.
591 Newman, S.W., 1999. The medial extended amygdala in male reproductive behavior. A node
592 in the mammalian social behavior network. Ann. N.Y. Acad. Sci. 877, 242-257.
593 Padilla, S.L., Qiu, J., Nestor, C.C., Zhang, C., Smith, A.W., Whiddon, B.B., Ronnekleiv,
594 O.K., Kelly, M.J., Palmiter, R.D., 2010. AgRP to Kiss1 neuron signaling links
595 nutritional state and fertility. Proc. Natl. Acad. Sci. 114, 2413-2418.
596 Pengelley, E.T., Fisher, K.C., 1957. Onset and cessation of hibernation under constant
597 temperature and light in the Golden-mantled ground squirrel (Citellus lateralis). Nature,
598 180, 1371-1372.
599 Pérez, J.H., Tolla, E., Bishop, V.R., Foster, R.G., Peirson, S.N., Dunn, I.C., Meddle, S.L.,
600 Stevenson, T.J., Functional inhibition of vertebrate ancient opsin facilitates photoperiod
601 induction of reproductive recrudescence in male Japanese quail. Unpublished.

602 Pérez, J.H., Tolla, E., Dunn, I., Meddle, S.L., Stevenson, T.J., 2019. A comparative
603 perspective on extra-retinal photoreception. Trends Endocrinol. Metab. 30, 39-53.
604 Perfito, N., Guardado, D., Williams, T.D., Bentley, G.E., 2015. Social cues regulate
605 reciprocal switching of hypothalamic Dio2/Dio3 and the transition into final follicle
606 maturation in European starlings (*Sturnus vulgaris*). Endocrinol. 156, 694-706.
607 Prendergast, B.J., 2010. MT1 melatonin receptors mediate somatic, behavioral and
608 reproductive neuroendocrine responses to photoperiod and melatonin in Siberian
609 hamsters (Phodopus sungorus). Endocrinol. 151, 714-721.
610 Roa, J. Herbison, A.E., 2012. Direct regulation of GnRH neuron excitability by arcuate
611 nucleus POMC and NPY neuron neuropeptides in female mice. Endocrinol. 153, 5587-
612 5599.
613 Ross, A.W., Russell, L., Helfer, G., Thomson, L.M., Dalby, M.J., Morgan, P.J., 2015.
614 Photoperiod regulates lean mass accretion, but not adiposity, in growing F344 rats fed a
615 high fat diet. PloS One 10, e0119763.
616 Sachs, B.D., 1967. Photoperiodic control of the cloacal gland of the Japanese quail. Science,
617 157, 201-203.
618 Saenz de Miera, C., Monecke, S., Bartzen-Sprauer, J., Laran-Chich, M.P., Pevet, P.,
619 Hazlerigg, D.G., Simonneaux, V., 2014. A circannual clock drives expression of genes
620 central for seasonal reproduction. Curr. Biol. 24, 1500-1506.
621 Sandrock, M., Schulz, A., Merkwitz, C., Schoneberg, T., Spanel-Borowski, K., Ricken, A.,
622 2009. Reduction in corpora lutea number in obese melanocortin-4-receptor-deficient
623 mice. Reprod. Biol. Endo. 7, 5412.
624 Satinoff, E., Valentino, D., Teitelbaum, P., 1976. Thermoregulatory cold-defense deficits in
625 rats with preoptic/anterior hypothalamic lesions. Brain Res. Bull. 1, 553-565.

626 Scheerlinck, J.P., Snibson, K.J., Bowles, V.M., Sutton, P., 2008. Biomedical applications of
627 sheep models: from asthma to vaccines. Trends Biotechnol. 26, 259-266.
628 Seminara, S.B., Messager, S., Chatzidaki, E.E., Thresher, R.R., Acierno, J.S. Jr, Shagoury,
629 J.K., BoAbbas, Y., Kuohung, W., Schwinof, K.M., Hendrick, A.G., Zahn, D., Dixon,
630 J., Kaiser, U.B., Slaugenhaupt, S.A., Gusella, J.F., O'Rahilly, S., Carlton, M.B.,
631 Crowley, W.F. Jr., Aparicio, S.A., College, W.H., 2003. The GPR54 gene as a regulator
632 of puberty. N Engl J Med. 349, 1614-1627.
633 Sharma, A., Singh, D., Das, S., Kumar, V., 2018. Hypothalamic and liver transcriptome from
634 two crucial life-history stages in a migratory songbird. Exp. Physiol. 103, 559-569.
635 Sharma, A., Kumar, V. 2019. Metabolic plasticity mediates differential responses to spring
636 and autumn migrations: Evidence from gene expression patterns in migratory buntings.
637 Exp Physiol. 104, 1841-1857.
638 Stevenson, T.J., Ball, G.F., 2009. Anatomical Localization of the Effects of Reproductive
639 State, Castration and Social Milieu on Cells Immunoreactive for Gonadotropin
640 Releasing Hormone – I in Male European Starlings (Sturnus vulgaris) J. Comp. Neurol.
641 517, 146-155.
642 Stevenson, T.J., Ball G.F., 2011. Information theory and the neuropeptidergic regulation of
643 seasonal reproduction in mammals and birds. Proc. R. Soc. 278:2477-2485.
644 Stevenson, T.J., Prendergast, B.J., 2013. Reversible DNA methylation regulates seasonal
645 photoperiodic time measurement. Proc. Natl. Acad. Sci. 110, 16651-16656.
646 Stevenson, T.J., Kumar, V., 2017. Neural control of daily and seasonal timing of songbird
647 migration. J. Comp. Physiol. A. 203, 399-409.
648 Stevenson, T.J., Hahn, T.P., MacDougall-Shackleton, S.A., Ball, G.F., 2012. Gonadotropin-
649 releasing hormone plasticity: a comparative perspective. Front. Neuroendocrinol. 33,
650 287-300.

651 Stevenson, T.J., Hahn, T.P. Ball, G.F., 2012b. Variation in gonadotrophin-releasing hormone-
652 1 gene expression in the preoptic area predicts transitions in seasonal reproductive state.
653 J. Neuroendocrinol. 24:267-274.
654 Stevenson, T.J., Bernard, D.J., McCarthy, M.M., Ball, G.F., 2013. Photoperiod-dependent
655 regulation of gonadotropin-releasing hormone 1 messenger ribonucleic acid levels in
656 the songbird brain. Gen Comp. Endocrinol. 1980, 81-87.
657 Stevenson, T.J., Prendergast, B.J., Nelson, R.J., 2017. Mammalian seasonal rhythms:
658 behavior and neuroendocrine substrates. In Hormone, Brain Behavior v3. Eds Pfaff &
659 Joels, Elsevier Sci (USA) Chap 19.
660 Tan, C.L., Knight, Z.A., 2018. Regulation of body temperature by the nervous system.
661 Neuron, 98, 31-48.
662 Tolla, E., Stevenson, T.J., 2020. Sex differences and the neuroendocrine regulation of
663 seasonal reproduction by supplementary environmental cues. Intr. Comp. Biol. 60,
664 1506-1516.
665 Trivedi, A.K., Kumar, J., Rani, S., Kumar, V., 2014. Annual life history-dependent gene
666 expression in the hypothalamus and liver of a migratory songbird: insights into the
667 molecular regulation of seasonal metabolism. J. Biol. Rhythms. 29, 332-345.
668 Trivedi, A.K., Malik, S., Rani, S., Kumar, V., 2015. Adaptation of oxidative phosphorylation
669 to photoperiod-induced seasonal metabolic states in migratory songbirds. Comp.
670 Biochem. Physiol. A Mol. Integr. Physiol. 184, 34-40.
671 Tsuruo, Y., Kawano, H., Kagotani, Y., Hisano, S., Daikoku, S., Chihara, K., Zhang, T.,
672 Yanaihara, N., 1990. Morphological evidence for neuronal regulation of luteinizing
673 hormone-releasing hormone-containing neurons by neuropeptide Y in the rat septo-
674 preoptic area. Neurosci. Letters, 110, 261-6.

675 Tsutsui, K., Ubuka, T., Bentley, G.E., Kriegsfeld, L.J., 2012. Gonadotropin-inhibitory
676 hormone (GnIH): discovery, progress and prospect. Gen. Comp. Endocrinol. 177, 304-
677 314.
678 Turi, G.F., Liposits, Z., Moenter, S.M., Fekete, C., Hrabovszky, E., 2003. Origin of
679 neuropeptide Y-containing afferents to gonadotropin-releasing hormone neurons in
680 male mice. Endocrinol. 144, 4967-4974.
681 Visser, M.E., 2008. Keeping up with a warming world; assessing the rate of adaptation to
682 climate change. Proc. Biol Sci. 275, 649-659.
683 Waterston, R.H. Pachter, L., 2002. Initial sequencing and comparative analysis of the mouse
684 genome. Nature, 420, 520-562.
685 Weaver, D.R., Rivkees, S.A., Reppert, S.M., 1989. Localization and characterization of
686 melatonin receptors in rodent brain by in vitro autoradiography. J. Neurosci. 9, 2581-
687 2590.
688 Weems, P.W., Goodman, R.L., Lehman, M.N., 2015. Neural mechanisms controlling
689 seasonal reproduction: principles derived from the sheep model and its comparison with
690 hamsters. Front. Neuroendocrinol. 37, 43-51.
691 Wingfield, J.C., Hahn, T.P., Wada, M., Schoech, S.J., 1992. Environmental predictability and
692 control of gonadal cycles in birds. J. Exp. Zool. 261, 214-231.
693 Wingfield, J.C., Williams, T., Visser, M.E., 2008. Integration of ecology and endocrinology
694 in avian reproduction: a new synthesis. Philos. Trans. R. Soc. Lond. B Biol. Sci. 363,
695 1581-1723.
696 Yamamura, T., Hirunagi, K., Ebihara, S., Yoshimura, T., 2004. Seasonal morphological
697 changes in the neuro-glial interaction between gonadotropin-releasing hormone nerve
698 terminals and glial endfeet in Japanese quail. Endocrinol. 145, 4264-4267.

699 Yasuo, S., Watanabe, M., Iigo, M., Yamamura, T., Nakao, N., Takagi, T., Ebihara, S.,
700 Yoshimura, T., 2006. Molecular mechanism of photoperiodic time measurement in the
701 brain of Japanese quail. Chronobiol. Inter. 23, 307-315.

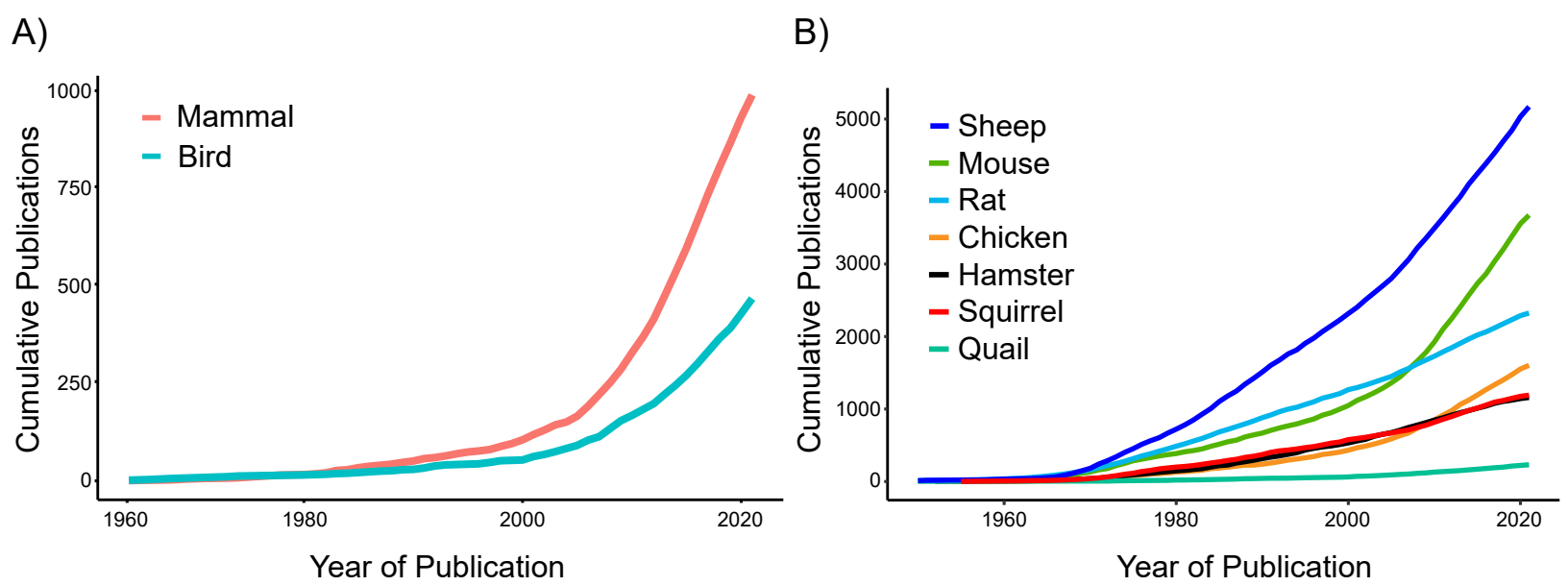
702

Figure legends

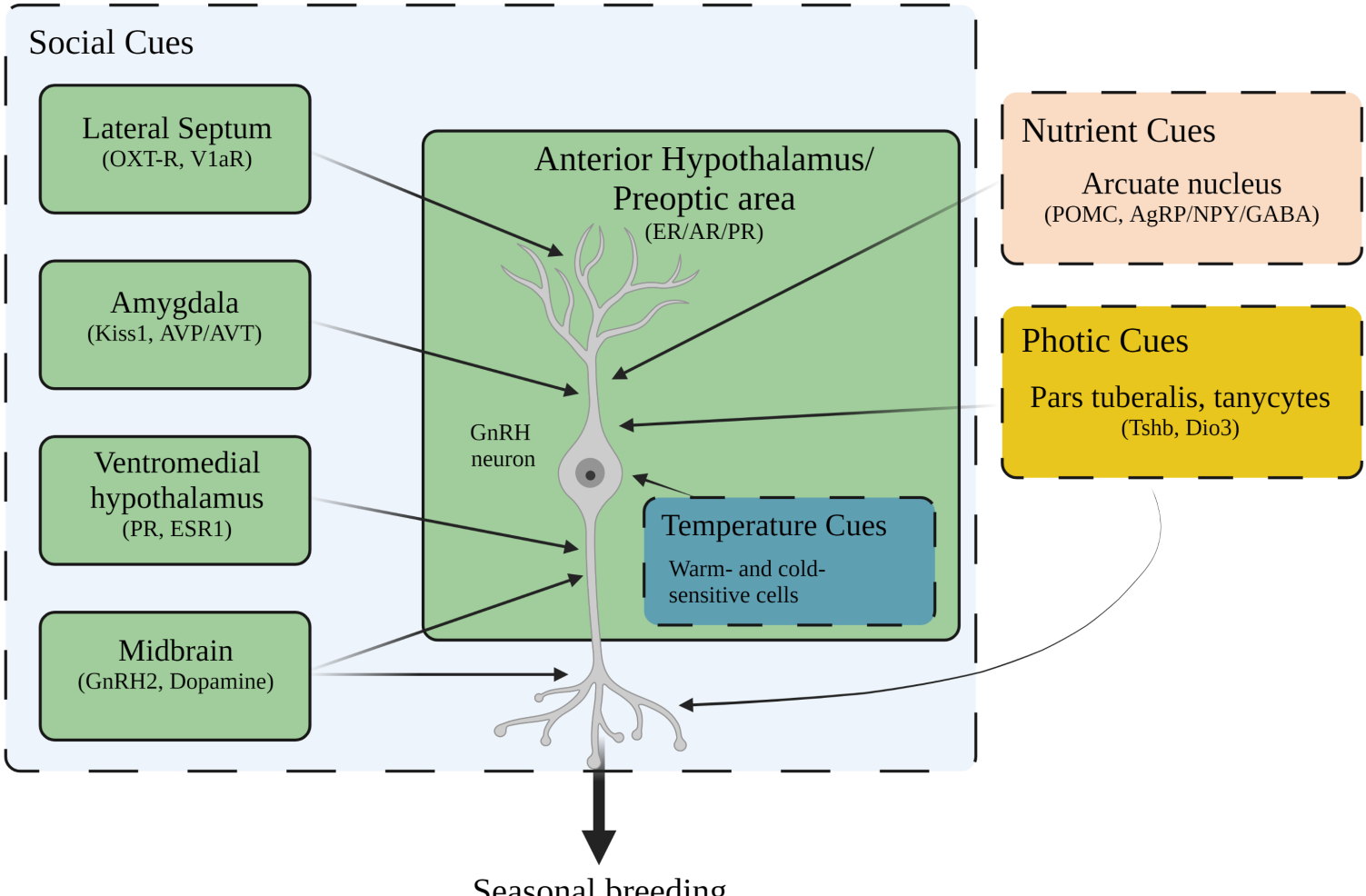
Figure 1 – PUBMED database for publications on seasonality in amniotes.
Analyses of search terms for 'seasonal' and 'mammal' or 'bird' indicates an exponential increase in the number of publications over the past 50 years (A). Break down of the number of publications for a select group of highly seasonal animals including sheep, mouse, rat, chicken, hamster, squirrel, and quail (B).

Figure 2 – Modular basis for the neural integration of environmental cues.
In both mammal and avian species, the pars tuberalis and median eminence integrate daylength cues and code photoperiodism. Environmental cues such as temperature, nutrient availability and social cues have some overlapping, but many distinct neural regions that guide seasonal timing of reproduction, body temperature, energy stability and sociality.

Figure 3 – Convergence of neural and cellular substrates on GnRH for seasonal rhythms in reproduction.
Gonadotropin-releasing hormone (GnRH) is an evolutionary conserved neuropeptide that controls reproduction in all vertebrates. GnRH neurons receive inputs from many neural substrates involved in the integration of social, temperature, nutrient and photic cues. Abbreviations: Agouti-related peptide (AgRP), Androgen receptor (AR), Arginine vasopressin (AVP), Arginine vasocotin (AVT), Deiodinase type-3 (Dio3), Estrogen receptor (ER), Gamma aminobutyric acid (GABA), Gonadotropin-releasing hormone-2 (GnRH-2), Kisspeptin-1 (Kiss1), Neuropeptide Y (NPY), Oxytocin receptor (OXT-R), Proopiomelanocortin (Pomc), Progesterone receptor (PR), Thyrotropin-stimulating hormone-β (Tshβ), Vasotocin 1a receptor (V1aR).


A)
Cumulative Publications
1000
750
500
250
0
Mammal
Bird
1960
1980
2000
2020
Year of Publication
B)
Cumulative Publications
5000
4000
3000
2000
1000
0
Sheep
Mouse
Rat
Chicken
Hamster
Squirrel
Quail
1960
1980
2000
2020
Year of Publication

Predictive cue	Supplementary cues		
Photoperiod	Temperature	Nutrients	Social cues
Pars tuberalis Median eminence	Anterior hypothalamus Preoptic area Dorsomedial hypothalamus	Arcuate nucleus Ventromedial hypothalamus Lateral hypothalamus Nucleus of the solitary tract	Amygdala Preoptic area Anterior hypothalamus Ventromedial hypothalamus Periaquaductal grey Lateral septum


Social Cues
Lateral Septum
(OXT-R, V1aR)
Amygdala
(Kiss1, AVP/AVT)
Ventromedial hypothalamus
(PR, ESR1)
Midbrain
(GnRH2, Dopamine)
Anterior Hypothalamus/ Preoptic area
(ER/AR/PR)
GnRH neuron
Temperature Cues
Warm- and cold-sensitive cells
Nutrient Cues
Arcuate nucleus
(POMC, AgRP/NPY/GABA)
Photic Cues
Pars tuberalis, tanycytes
(Tshb, Dio3)
Seasonal breeding