COMMENTARY

A possible role of perinatal light in mood disorders and internal cancers: Reconciliation of instability and latitude concepts

Thomas C. Erren [1], Melissa S. Koch [1], J. Valérie Gross [1], Russel J. Reiter [2], V. Benno Meyer-Rochow [3]

1 Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University of Cologne, Lindenthal, Germany
2 Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
3 School of Engineering and Science; Jacobs University Bremen, Germany

Correspondence to: Prof. Thomas C. Erren, MD., MPH.
Director of the Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University of Cologne, Lindenthal, Germany.
tel: +49-221-4784450; fax: +49-221-4785119; e-mail: tim.erren@uni-koeln.de

Submitted: 2012-04-17 Accepted: 2012-04-24 Published online: 2012-05-27

Key words: **light; perinatal; circadian clocks; circadian systems; mood disorder; cancer; latitude; melatonin; childhood disease; adult disease**

Neuroendocrinol Lett 2012; **33**(3):314–317 **PMID:** 22635091 NEL330312L02

Abstract

Thought-provoking experimental evidence suggests that perinatal light exposure may imprint circadian clocks with lasting effects on the alignment and the stability of circadian rhythms later in life. Assuming that exposure to light early in life could determine the stability of an individual's circadian system later in life, the present hypothesis proposes that time of year and location of birth (i.e., season and latitude) and thus differential *Zeitgeber* strengths may be key contributors to a person's susceptibility of developing mood disorders like seasonal affective disorder (SAD) and common internal cancers such as those of breast and prostate. Consequently, when and where people are born might critically predispose them to both mood disorders and internal cancers, and may affect the onset and course of such illnesses. This paper develops a causal framework and presents suggestions for rigorous tests of the associated corollary and predictions.
It does not escape our attention that links between the perinatal *Zeitgeber* strength of light and its effects on the stability of circadian systems later in life could have a role to play in affecting long-term health beyond cancer and mood disorders – mostly in adults but also in children.

INTRODUCTION

A recent report in *Nature Neuroscience* (Ciarleglio *et al.* 2011) can provide the basis for a comprehensive new hypothesis on the development of mood disorders (Erren *et al.* 2011a) and internal cancers (Erren *et al.* 2011b). Ciarleglio *et al.* deduce from their experiments in mice that perinatal exposure to light can have an imprinting effect insofar as stable or unstable circadian systems will become established. When mice were developed and raised until weaning (day 21 after birth) under winter-light conditions, i.e., L:D 8:16 or short days, they developed unstable circadian systems which could be disturbed by light exposure at unusual times later in their lives. Among the observed consequences were behavioral peculiarities. The authors concluded that their findings might

point to a link between perinatal imprinting of circadian clocks and neurobehavioral disorders in humans.

Importantly, this is not the first report of the kind (Ohta *et al.* 2006). In 2006, Ohta *et al.* asked what light exposure might do to neonates in intensive care units. They addressed this question by exposing mice postnatally, i.e., after birth for four weeks, to constant light (L:D 24:0). After postnatal exposure to these extreme lighting conditions, the rodents exhibited signs of disrupted internal temporal order and developed unstable circadian organization later in life. Since this earlier experiment comprised longer observation periods of over several months, the lasting effects of the postnatal light intervention may be interpreted as a demonstration of imprinting.

Circumstantial evidence that postnatal light exposure might contribute to a developmental imprinting of circadian clocks and systems comes from further experimental observations: intrinsically photosensitive retinal ganglion cells (ipRGCs) respond to light from birth onward (Hannibal & Fahrenkrug 2004; Sekaran *et al.* 2005) and these ipRGCs appear to make an until 2011 unrecognized contribution to the development of the central visual system (Renna *et al.* 2011), presumably including interfaces with circadian circuitry.

WHY INSTABILITY AND WHY LATITUDE CONCEPTS?
—
BACKGROUND AND RECONCILIATION

The importance of the cyclic nature of circadian and biological organization, and their stability, was emphasized by Colin Pittendrigh over half a century ago (Pittendrigh 1960):

> *… circadian rhythms are inherent in and pervade the living system to an extent that they are fundamental features of its organization; and to an extent that if deranged they impair it.*

The 1960 Cold Spring Harbor Symposium on "Biological Clocks" may be viewed as the cradle of modern chronobiology. The 2007 Cold Spring Harbor Symposium on "Clocks and Rhythms" demonstrated that recent decades have – at an increasing pace – brought interest in, and elucidation of, many causal details regarding the nexus of circadian biology, health and disease (Menaker 2007), and the key role that light plays as the dominant *Zeitgeber* (Aschoff 1951; 1954; Erren *et al.* 2003).

The next logical step was to zero in on ways to test hypotheses with regard to light on the one hand, and health and disease in man on the other. Looking at endpoints such as mood disorders (Goodwin & Jamison 1990; Potkin *et al.* 1986) and internal cancers (Erren & Piekarski 1999; Erren & Reiter 2008) highlights the need to investigate long-term processes which lead or contribute to these diseases over many years, sometimes decades. This directed research to epidemiological studies that aimed at comparing populations exposed to more or less amounts of light over extended periods. Turning to studies which employed "latitude" meant making use of "natural experimental conditions", in which "light dosimetry by geography" (Erren *et al.* 2001) approaches employed variable ambient photoperiods due to latitude-associated angles at which sunlight exposes locations on Earth differentially (Erren 2002). Latitude was thus a means to differentiate doses of natural light exposures. How unequal doses of environmental light may actually contribute to a deranged circadian organization is now evinced by the results reported by Ciarleglio and colleagues (2011): Perinatal winter or summer photoperiods appear to imprint stable or unstable responses of mammals' circadian systems to changes in light/dark transitions later in life.

Overall, therefore, instability and latitude concepts may now be reconciled by their common denominator, "light", which early in life may imprint the very stability of circadian systems and may later in life constitute a disturbance variable to circadian and seasonal rhythmicity when experienced at biologically unusual times.

HYPOTHESIS, COROLLARY, PREDICTIONS & TESTS

H Humans born and raised postnatally under winter light conditions with low *Zeitgeber* strength where the amplitude of the L:D-cycle entraining circadian clocks is small, i.e., close to 0.5, are more likely to develop unstable circadian clocks and systems later in life than humans exposed to comparatively higher perinatal L:D ratios, i.e., close to 2.

C At extreme latitudes, we can expect more babies to be born during periods of extreme light/dark ratios such as ≤0.5 during winter seasons, than at lower latitudes. We expect those born at extreme latitudes shortly before or during extended winter months to have increased risks of developing unstable – rather than robust – circadian systems.

Assuming that the corollary is correct, four predictions can be formulated for rigorous testing within epidemiological cohort and case-control studies:

$P_1|C$ SAD rates in cohorts of individuals born in winter months at extreme latitudes are higher than in cohorts born at other times of the year and/or in locations closer to the Equator.

$P_2|C$ The likelihood of having been born in winter months and at extreme latitudes is higher in cases with SAD than in controls without the disorder.

$P_3|C$ Internal cancer rates in cohorts of individuals born in the winter months at extreme latitudes are higher than in cohorts born at other times of the year and/or locations closer to the Equator.

$P_4|C$ The likelihood of having been born in winter months and at extreme latitudes is higher in cases with internal cancer than in controls without the disease.

Two additional considerations are in order here:

First, exposure to light-at-night [LAN] should not alter the perinatal *Zeitgeber* strength. Throughout the year, we expect protection against natural and anthropogenic LAN because newborns are shielded from light during bedrest (Erren 2002). Moreover, with closed eyelids, light intensities between 1700 and 2000 lux do not lead to melatonin suppression (Hatonen *et al.* 1999; Jean-Louis *et al.* 2000).

Second, based on the limited empirical information on possible links between perinatal Zeitgeber strength and an imprinting of circadian system stability, L:D ratios examined (Ciarleglio *et al.* 2011; Ohta *et al.* 2006), i.e., 8:16, 12:12, 16:8, and 24:0, would take on the value range $0.5 \leq 1 \leq 2 < 24$. While it may take many years to understand the details, L:D 12:12 may be a reference point in humans as has been in the study by Ciarleglio *et al.* for mice. This would render low and high *Zeitgeber* strengths to correspond with L:D ratios below or above 1 and close to 0.5 and 2, respectively.

OLD TESTS OF THE NEW HYPOTHESIS?

Clearly, the question arises whether the proposed hypothesis has been tested earlier, deliberately or somewhat circumstantially. Equally clearly, the answer is "no".

We should not confuse studies that looked at the occurrence of mood disorders and internal cancers in adults in connection with "instability" *or* "latitude": whether the disease endpoints distribute differentially with regard to circadian stability or geographic location alone is not what we hypothesize. A few studies investigated a possible role of season of birth and photoperiod for the development of disease. However, in these studies the hypothesized links were based on the role of light possibly affecting the stability of circadian systems or the production of melatonin (Erren & Piekarski 1999) over decades.

But this paper's reference point is *not* where study participants lived over decades and what light exposures they experienced there, but rather where they were born and what the perinatal photoperids were at the time. To capture the possibly critical time when the very stability or instability of our circadian systems may be determined, we likely have to extend the time window of interest, for instance to three months before and three months after birth. To the best of our knowledge, such (peri)natal light exposures have not been systematically examined in observational research as a possible determinant for disease endpoints such as mood disorders or internal cancers.

Overall, since there are merely scattered studies which looked at either season of birth *or* latitude, but not at season of birth *and* latitude to assess the possible role of perinatal photoperiod on the development of adult disease, we still lack tests of the new hypothesis.

PERSPECTIVES

Rigorous epidemiological tests of our hypothesis and associated predictions can be conducted both time- and cost-effectively in two ways: by revisiting completed studies or by pursuing new studies which include as explanatory variables, namely the "when" and "where" individuals were born, in their risk analyses (Erren *et al.* 2011a,b).

If epidemiological studies were to lend support to our hypothesis, we would have promising angles to act on light:dark exposure patterns and influence the development of circadian stability in (a) late pregnancy, (b) at birth and (c) after birth.

More generally, with a better understanding of how L:D cycles affect perinatal development, we could treat children born both prematurely and at-term with ideal L:D ratios as a means of prevention against illnesses that are common later in life.

More specifically, the objective should be to optimize cylic L:D ratios in (a), (b) and (c). In this vein, both pregnant and breast-feeding mothers' melatonin may play a key role for the development of the perinatal circadian time-keeping system by relating it to environmental signals (Illnerova *et al.* 1993; Cubero *et al.* 2005).

That melatonin has a physiological role with regard to synchronizing seasonal functions is beyond dispute (Simonneaux 2011). Importantly, recent experiments suggest that melatonin signals determine daily functions as well via entraining circadian clocks in rats in fetal life (Torres-Farfan *et al.* 2011). Overall, it was commented that "data indicate that newborn animals are sensitive to the photoperiodic history encountered during the prenatal period and that maternal melatonin may be the clock/calendar signal that primes the developing biology of the fetus during the prenatal period" (Simmonneaux 2011; Reiter 1993).

Moreover, for both prematurely born children, in particular those needing extensive care or other hospital help, or for children born at-term, we may want to arrange for cyclic L:D ratios which suggest to their developing circadian systems that they are raised under long-day conditions with high *Zeitgeber* strength, i.e., a large amplitude of L:D-cycles such as 16:8.

Almost one decade ago, the general concept of "chronodisruption" was proposed "as a relevant disturbance of orderly biological rhythms over days and seasons and years in man" and it was suggested that "causes and course of aging and cancers can be considered as being both light- and rhythm-related" (Erren *et al.* 2003). When chronodisruption [CD] was further defined in 2008 (Erren & Reiter 2008), the following key question

was identified: "How can we appropriately investigate CD and its effects in experimental and in epidemiological studies?"

In closing, it does not escape our attention that what we suggest in this paper provides one possible answer to the latter question: By considering the "when" and "where" individuals were born we may recognize and include a perinatal signature of light (Erren *et al.* 2012) as indicator of the very susceptibility of circadian systems to be disrupted later in life.

Nor does it escape our attention that links between the perinatal *Zeitgeber* strength of light and its effects on the stability of circadian systems later in life could have a role to play in affecting long-term health beyond cancer and mood disorders – mostly in adults but also in children (Erren 2005).

Conflict of Interest

None.

REFERENCES

1 Aschoff J (1951). Die 24-Stunden-Periodik der Maus unter konstanten Umgebungsbedingungen. Naturwissenschaften **38**: 506–507.
2 Aschoff J (1954). Zeitgeber der tierischen Tagesperiodik. Naturwissenschaften **41**: 49–56,
3 Ciarleglio CM, Axley JC, Strauss BR, Gamble KL, McMahon DG (2011). Perinatal photoperiod imprints the circadian clock. Nat Neurosci. **14**: 25–27.
4 Cubero J, Valero V, Sanchez J, *et al.* (2005). The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. Neuro Endocrinol Lett. **26**: 657–661.
5 Erren TC (2002). Does light cause internal cancers? The problem and challenge of an ubiquitous exposure. Neuro Endocrinol Lett. **23** Suppl 2: 61–70.
6 Erren TC (2005). Could visible light contribute to the development of leukaemia and other cancers in children? Med Hypotheses. **64**: 864–871.
7 Erren TC, Piekarski C (1999). Does winter darkness in the Artic protect against cancer? The melatonin hypothesis revisited. Med Hypotheses **53**: 1–5.
8 Erren TC, Reiter RJ (2008). A generalized theory of carcinogenesis due to chronodisruption. Neuro Endocrinol Lett. **29**: 815–821.
9 Erren TC, Reiter RJ (2008). Defining chronodisruption. J Pineal Res. **46**: 245–247.
10 Erren TC, Bjerregaard P, Cocco P, Lerchl A, Verkasalo P (2001). Re: "Invited commentary: electromagnetic fields and cancer in railway workers. Am J Epidemiol. **154**: 977–979.
11 Erren TC, Reiter RJ, Piekarski C (2003). Light, timing of biological rhythms, and chronodisruption in man. Naturwissenschaften **90**: 485–494.
12 Erren TC, Nise MS, Meyer-Rochow VB (2011a). Latitude, light, clocks and mood. Psychopharmacology (Berl) **216**: 147–148.
13 Erren TC, Gross JV, Meyer-Rochow VB (2011b). Light, Clocks, Mood, and Cancer: Consolidation and Novel Tests of Latitude and Instability Hypotheses. Chronobiol Int. **28**: 471–473.
14 Erren TC, Koch MS, Gross JV, Meyer-Rochow VB (2012). Do Perinatal Photoperiods Imprint Human Chronobiology? Suggestion for a study into the possible signature of light in the Northern and Southern Hemispheres. Chronobiol Int. **29**: 371–372.
15 Goodwin FK, Jamison KR (1990). Sleep and biological rhythms. In Manic-depressive illness, 1st ed. New York: Oxford University Press, pp. 541–574.
16 Hannibal J, Fahrenkrug J (2004). Melanopsin containing retinal ganglion cells are light responsive from birth. Neuroreport **15**: 2317–2320.
17 Hatonen T, Alila-Johansson A, Mustanoja S, Laakso ML (1999). Suppression of melatonin by 2000-lux light in humans with closed eyelids. Biol Psychiatry **46**: 827–831.
18 Illnerova H, Buresova M, Presl J (1993). Melatonin rhythm in human milk. J Clin Endocrinol Metab. **77**: 838–841.
19 Jean-Louis G, Kripke DF, Cole RJ, Elliot JA (2000). No melatonin suppression by illumination of popliteal fossae or eyelids. J Biol Rhythms **15**: 265–269.
20 Menaker M (2007). Circadian clocks: 50 years on. Cold Spring Harb Symp Quant Biol. **72**: 655–659.
21 Ohta H, Mitchell AC, McMahon DG (2006) Constant light disrupts the developing mouse biological clock. Pediatr Res. **60**: 304–308.
22 Pittendrigh CS. (1960). Circadian rhythms and the circadian organization of living systems. Cold Spring Harb Symp Quant Biol. **25**: 159–184.
23 Potkin SG, Zetin M, Stamenkovic V, Kripke D, Bunney WE, Jr. (1986). Seasonal affective disorder: prevalence varies with latitude and climate. Clin Neuropharmacol, **9** (Suppl 4): 181–183.
24 Reiter RJ (1993). The melatonin rhythm: both a clock and a calendar. Experientia **49**: 654–664.
25 Renna JM, Weng S, Berson DM (2011). Light acts through melanopsin to alter retinal waves and segregation of retinogeniculate afferents. Nat Neurosci. **14**: 827–829.
26 Sekaran S, Lupi D, Jones SL, Sheely CJ, Hattar S, Yau KW, *et al.* (2005). Melanopsin-dependent photoreception provides earliest light detection in the mammalian retina. Curr Biol. **15**: 1099–1107.
27 Simonneaux V (2011). Naughty melatonin: how mothers tick off their fetus. Endocrinology. **152**: 1734–1738.
28 Torres-Farfan C, Mendez N, Abarzua-Catalan L, Vilches N, Valenzuela GJ, Seron-Ferre M (2011). A circadian clock entrained by melatonin is ticking in the rat fetal adrenal. Endocrinology. **152**: 1891–1900.