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ORIGINAL ARTICLE

Immediate effect of blue-enhanced light on reproductive hormones in women

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Abstract

OBJECTIVE: Light is known to stimulate reproductive function in women. We here investigated the immediate effect of light on reproductive hormones, addressing the role of blue-sensitive (~480 nm) melanopsin-based photoreception mediating the non-visual effects of light.

METHODS: Sixteen healthy women attended the Institute at ~07:25 (shortly after waking; sunglasses worn) twice in 2–3 days in April–May, within days 4–10 of their menstrual cycle. During one session, a broad-spectrum white-appearing light with a superimposed peak at 469 nm was presented against 5–10 lux background; during the other session, short-spectrum red light peaked at 651 nm with similar irradiance level (~7.0 W/m^2, corresponds to ~1200 lux) was used. Venous blood was taken at 0, 22 and 44 minutes of light exposure to measure concentrations of follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin, estradiol, progesterone and cortisol, and saliva was sampled to measure melatonin as a recognised indicator of the spectral-specific action of light.

RESULTS: Melatonin values, as expected, were lower with white vs. red light (p=0.014), with the greatest difference at 22 minutes. Of the other hormones, only FSH concentrations differed significantly: they were mildly higher at white vs. red light (again, at 22 minutes; p=0.030; statistical analysis adjusted for menstrual cycle day and posture change [pre-sampling time seated]).

CONCLUSION: Moderately bright blue-enhanced white light, compared to matched-by-irradiance red light, transiently (within 22 minutes) and mildly stimulated morning secretion of follicle-stimulating hormone in women in mid-to-late follicular phase of their menstrual cycle suggesting a direct functional link between the light and reproductive system.

Abbreviations:

GnRH	- Gonadotropin-releasing hormone
FSH	- Follicle-stimulating hormone
LED	- Light-emitting diode
LH	- Luteinising hormone
rANOVA	- Analysis of variances for repeated measures
SD	- Standard deviation (of the mean)

INTRODUCTION

Light – natural or artificial – acting via the eyes, is known to stimulate reproductive function in women (summarised in Danilenko & Samoilova 2007; Danilenko *et al.* 2011). As an important part of these effects, morning bright light presented daily, increases blood concentration of follicle-stimulating hormone (FSH) and/or luteinising hormone (LH) (Danilenko & Samoilova 2007; Kripke *et al.* 2010). The mechanism of this action is unknown. It may involve immediately signaling neuronal pathways and a slower endocrine feedback loops (e.g. via melatonin, Liu *et al.* 2013). The neuronal pathways for the physiological effects of light include blue-sensitive (~480 nm) melanopsin-based photoreceptive ganglion cells synapsing hypothalamic and other brain regions (LeGates *et al.* 2014). This mediates the 'non-image-forming' effects of light: circadian phase shifting, melatonin suppression, pupillary constriction, alertness enhancement, mood improvement (LeGates *et al.* 2014). Whilst melatonin secretion is exclusively neuronal-dependent, it is suppressed very quickly (within 5–10 minutes; Petterborg *et al.* 1991) by blue light and is not influenced by red light or darkness (Brainard *et al.* 1985, 2001; Thapan *et al.* 2001). Little is known about the immediate effect of light on the reproductive hormones.

Miyauchi *et al.* (1990) investigated the effect of a light stimulus 3000 lux presented between 22:40 and 24:00 on five women in their follicular phases and found an increase of LH and FSH compared to pre-stimulus levels 21:30–22:40; in the reference group of six participants without light, the hormone concentrations did not change. In a subsequent study (Miyauchi *et al.* 1991), the serum concentration of FSH was increased at 02:00 (n=17) following light stimulus 500–800 lux presented from 17:30 to 02:00; the rise of LH was not significant. The findings on prolactin – the third hypophyseal reproductive hormone – are contradictory in healthy participants: blood prolactin concentrations were augmented (Miyauchi *et al.* 1990); unaffected (Byerley *et al.* 1988; McIntyre *et al.* 1992; Kostoglou-Athanassiou *et al.* 1998); or suppressed (Bispink *et al.* 1990; Miyauchi *et al.* 1991; Okatani & Sagara 1993) during evening/night exposure. Night-time estradiol concentrations were found unchanged in 22 women exposed to bright light 5200 lux from 21:00 to 01:00 (Graham *et al.* 2001).

We here investigated the immediate impact of light on reproductive hormones in women, specifically addressing the role of the blue-sensitive retina-brain connection. In addition to hypophyseal hormones, ovarian hormones estradiol and progesterone were assayed as, hypothetically, the ovary secretion may be rapidly influenced via the hypothalamus-ovary neurovegetative pathway demonstrated in rats (Tóth *et al.* 2008). Melatonin and cortisol were measured (control) as recognised indicators of the spectral-specific action of light (Brainard *et al.* 1985, 2001; Thapan *et al.* 2001) and of stress reaction (e.g. Keitel *et al.* 2011), respectively.

MATERIALS AND METHODS

Participants

The study was approved by the Ethics Committee of the Institute of Internal and Preventive Medicine, registered at ClinicalTrials.gov (NCT00467805), and performed in April–May 2009. The volunteers were recruited via advertisements around the Institute and by 'word of mouth'. The participants had to be women aged 18–45 years with regular menstrual cycles between 21–35 days (as verified by individual logs), relatively healthy; with body mass index between 18.5–29.9 kg/m^2, not under medication; with normal regimen of sleep-wakefulness; and living within 10-min walk distance from the Institute. The subjects were recruited during the selection visits by both study physicians (KVD and OYS). All participants gave written informed consent and were paid for the participation.

Study protocol

The participants came to the unit twice in 2–3 days (weekends usually excluded) during the mid-follicular phase calculated from their menstrual cycle length (Danilenko *et al.* 2011). They arrived at ~07:25 shortly after waking, fast (only water was allowed) and wore sunglasses (light intensity <10 lux at the eye level) during the 5–10 minute walk from their home to the Institute (dawn time range 04:59–06:19). After arriving, participants remained seated for ~50 minutes during which bright light was presented for 45 minutes against dim room background (5–10 lux at the direction of gaze). During one session, a white light with a superimposed peak at 469 nm was presented; during the other session red light of similar irradiance level was used (crossover, alternate order). Venous blood (~5 ml) and saliva (~1.5 ml) was sampled immediately prior to and at 22 and 44 minutes of light exposure.

Intervention

Lumie SADlight device with LEDs (Cambridge, UK; www.lumie.com; aperture size 10.8×6.0 cm) emitted white-appearing light of intensity 1300 lux at the distance of 50 cm. The same unit fitted with red LEDs was used as the control and emitted red light of intensity 1100 lux at a distance of 45 cm. The irradiance levels were similar (~7.0 W/m^2) at the distance stated (irradiance, irrespective of illuminance, does not account for the human eye sensitivity). The less powerful red light device was positioned only slightly closer as red light appeared to be less divergent than white light. It was not necessary to look at the device all the time, just to allow light to freely enter both eyes.

Figure 1 shows relative spectral power distribution of the white and red lights measured at the given distances against the ambient light of 5 lux (firm "Afalina", Novo-

sibirsk; irradiance detector with the head partly cosine-corrected for the illuminance). The broad-spectrum white light has a superimposed peak at 469 nm. Short-spectrum red light peaked at 651 nm. Areas under the curves (analysed range 400–750 nm) confirmed similar photon doses for white and red lights: 54'660 and 56'410 arbitrary units, respectively.

Variables analysed and statistics

Blood serum and saliva samples were kept frozen until the hormonal assay. Serum was measured by enzyme-linked immunosorbent assay (ELISA) for concentrations of LH, FSH, prolactin, cortisol, progesterone (reagent kits obtained from AlcorBio, http://www.alkorbio.ru) and for estradiol (reagent kits obtained from DRG, http://www.drg-diagnostics.de). Saliva was measured for concentrations of melatonin by radioimmunoassay in Bühlmann Laboratories using reagent Bühlmann kits (http://www.buhlmannlabs.ch). The samples from each individual were assayed in the same batch to avoid inter-assay variability. The functional sensitivity of the assay and intra-assay variations (within the normal range of hormone) were as follows: 0.25 U/l and <8% for LH, 0.25 U/l and <8% for FSH, 2.36 ng/ml and <8% for prolactin, 5 nmol/l and <8% for cortisol, 0.5 nmol/l and <8% for progesterone, 9.7 pg/ml (analytical sensitivity) and <6.8% for estradiol, 0.9 pg/ml and 2.6–20.1% for melatonin.

Participants kept a diary that included timing of night sleep episodes starting from the 1st day of the menstrual cycle. On the study days, chronology of morning events (getting up, leaving home, arrival at the Institute, being seated, blood/saliva sampling) was recorded.

The primary statistics in the study was Student's paired t-test or analysis of variances for repeated measures (rANOVA). In rANOVA, the yielded Huynh-Feldt's corrected probability (p) was considered for the significance. StatView 5.0.1 and SPSS 21.0 softwares were used.

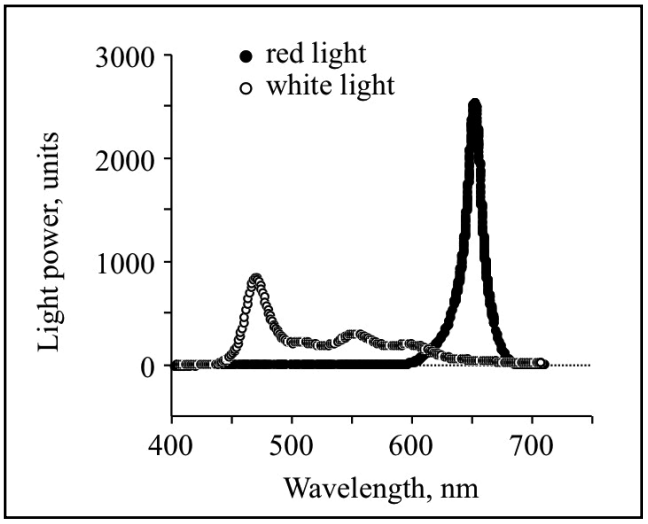

Fig. 1. Spectral composition of red and white lights.

RESULTS

Baseline data

In total, 16 women entered the study and all completed (Table 1). White light happened to be used in the first session more often than red light (10 vs. 6 times). Menstrual cycle day; getting up time; time of the arrival to the study room; time seated prior to the light exposure did not differ significantly between the white and red light session in the group (Table 1).

Hormonal values were generally within the normal range, except one woman (42 years) with consistently, though moderately, raised LH, FSH and estradiol (less than 2.5 times the upper limit) and another woman (22 years) with LH mildly above the norm. Pre-exposure prolactin concentrations in the group were sometimes almost 3 times the upper limit but then rapidly declined which was obviously circadian-dependent.

Tab. 1. Characteristics of the study group.

Variable	Mean ± SD (range), median (range) or number n		
Number of women	16		
Age, years	28.0 ± 7.2 (20–44)		
Days between sessions	2 (n=11) or 3 (n=5)		
	Red light	White light	difference
First session, n	6	10	
Menstrual cycle day	7 (4-10)	6 (4-10)	2 days: n=11 3 days: n=5
Getting up time	06:55 ± 10 min (06:30–07:12)	06:52 ± 9 min (06:30–07:00)	3 ± 12 min (-23 to 33)
Arrival (taking a seat) time	07:27 ± 11 min (07:09–07:53)	07:26 ± 9 min (07:13–07:48)	1 ± 10 min (-17 to 18)
Pre-sampling time seated, min	4.9 ± 1.9 (3–8)	5.0 ± 3.0 (2–14)	-0.1 ± 2.4 (-6 to 4)

Outcomes and estimation

Pre-exposure hormone values did not differ between the white and red light sessions (Table 2; $p>0.15$, Student test). As for the sequence effect, pre-exposure concentrations of estradiol were higher and FSH lower ($p=0.027$ and $p=0.076$, respectively, Student test) at the second session reflecting normal hormones dynamics during the follicular phase (Hayes *et al.* 1998). The pre-exposure values differed by 1.3–2.7 times within individuals (and much more inter-individually) and correlated significantly with the subsequent change in almost all hormones (higher initial values resulted in greater differences between 1st and 2nd measurements). As this might compromise results of the further analysis, hormone values were expressed as a percentage with the initial value assigned to 100%.

Dynamics of the hormone values are shown in Figure 2. All hormone concentrations decreased during the first 20 minutes of the intervention period (rANOVA, factor 'time', $p\leq0.05$), and melatonin, prolactin and cortisol values continued to decrease during the next 20 minutes ($p<0.0001$). This may reflect the natural morning decay (circadian-dependent for melatonin and prolactin or following the post-awakening peak for cortisol; Caufriez *et al.* 2009). However, data on the remaining hormones (that do not exhibit circadian variations; Caufriez *et al.* 2009) suggest that this decrease is due to a known posture change from upright to sitting position that lasts for 20 minutes (Hagan *et al.* 1978; Deacon & Arendt 1994).

To account for the possible confounding influence of posture and menstrual cycle on the effects of white vs. red light on the hormone concentrations, a difference

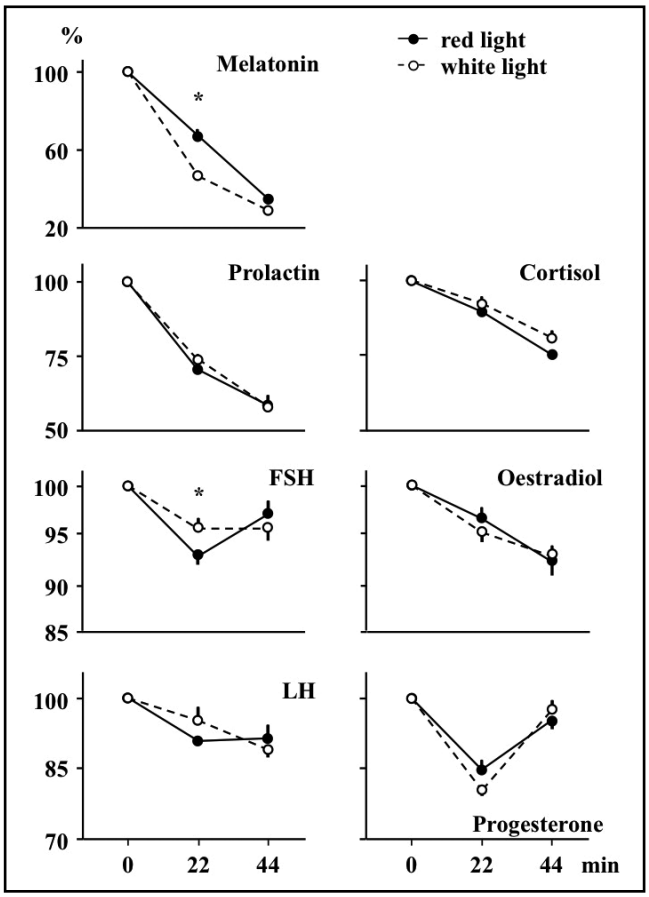

Fig. 2. Dynamics of the hormone values. The pre-exposure values (at 0 minutes, corresponds to ~07:40) were assigned to 100%. Values at 22 and 44 minutes were adjusted for menstrual cycle day and posture change (time seated) using ANCOVA. Whiskers represent standard errors of the means, * - significant ($p<0.05$) difference between the values at white and red light sessions.

Tab. 2. Hormone values (medians and, in parenthesis, the 10th and 90th percentiles, n=16).

Hormone	Light	Time (min)		
		0	22	44
Melatonin, pg/ml	red	8.8 (2.8–15.4)	5.1 (1.6–11.4)	2.7 (0.5–8.7)
	white	8.3 (3.7–24.9)	3.6 (1.1–11.9)	3.2 (0.3–8.4)
Prolactin, ng/ml	red	23.7 (13.6–50.4)	18.6 (9.7–30.3)	15.0 (7.4–22.2)
	white	20.6 (14.4–36.8)	14.6 (11.8–25.4)	12.4 (8.3–17.6)
FSH, U/l	red	8.1 (6.0–11.0)	7.8 (5.2–9.8)	8.3 (5.6–11.7)
	white	7.9 (6.1–19.7)	7.6 (6.0–18.1)	7.4 (5.6–17.4)
LH, U/l	red	6.5 (3.6–15.3)	5.7 (3.3–13.1)	5.1 (3.3–10.8)
	white	6.4 (3.8–12.9)	5.9 (3.7–13.2)	4.9 (3.5–11.7)
Oestradiol, pg/ml	red	35.3 (26.1–108.5)	34.5 (23.3–95.8)	33.8 (23.4–85.2)
	white	33.2 (25.4–149.5)	30.0 (24.2–133.0)	30.1 (24.7–128.0)
Progesterone, nmol/l	red	6.7 (4.3–15.3)	6.3 (3.9–13.9)	7.4 (4.3–13.1)
	white	7.6 (3.2–13.5)	6.2 (2.4–11.1)	7.6 (3.7–11.4)
Cortisol, nmol/l	red	640 (479–842)	617 (395–707)	478 (372–631)
	white	638 (510–763)	581 (436–763)	501 (367–641)

between the two light sessions in pre-exposure time seated and in menstrual cycle day (Table 1), as well as their interaction term, has been routinely introduced as covariates to the rANOVA. As expected, there was a more pronounced drop in melatonin values with white vs. red light (rANOVA's p=0.014), attaining a significant difference specifically at the second time point (46.7% vs. 67.6%, rANOVA's p=0.014) and becoming negligible at the third time point (29.0% vs. 35.0%, rANOVA's p=0.20). No significant effect of factor 'light' was observed for other hormones.

Nevertheless, factor 'light' interacted with factors 'time seated' and 'menstrual cycle' in the analysis of its effect on the FSH dynamics (rANOVA's p=0.087 and p=0.001, respectively). Taking into account a short-lasting (within 20 minutes) effect of posture change on the hormone concentration, an rANOVA for each time point (at 22 and 44 minutes) separately was performed. The analysis revealed higher FSH values with white vs. red light at 22 minutes (95.8% vs. 92.7%, rANOVA's p=0.030).

Steady correlations (persisting in analysis of hormonal % values at 22 and 44 minutes separately and after control of outliers) were observed between FSH and LH and those between FSH and prolactin (p<0.02, Spearman test, n=32). One more correlation that was persistent was between prolactin and cortisol (p<0.03, Spearman test, n=32); all correlations direct.

DISCUSSION

Basic findings

Morning secretion of FSH was transiently (within 20 minutes) and mildly higher during the blue-enhanced white light exposure, compared to the matched-by-irradiance red light. No significant spectrum-related changes were found for other reproductive hormones (prolactin, LH, estradiol, progesterone) in the experimental conditions.

Melatonin values were found to be lower with white vs. red light confirming a different effect of study conditions on brain physiology as melatonin suppression is mediated via melanopsin photoreceptors in the eye that are sensitive to blue, not red light (Brainard *et al.* 2001; Thapan *et al.* 2001). Though melatonin suppression is usually sustained throughout the period of light exposure (e.g. Byerley *et al.* 1988), the difference was significant at the 22nd minute; at the 44th minute the melatonin concentration (median=3.2 pg/ml) may have been too low to meet significance since melatonin production naturally ceases in the morning to a stable daytime level of 0–1 pg/ml.

FSH

Conversely to melatonin, FSH values were higher with white vs. red light, following the first 22 minutes of light presentation, confirming an inverse relationship between melatonin and gonadal axis activity that is more evident in animals (Reiter *et al.* 2009; Tamura *et al.* 2014) than in humans (Kripke *et al.* 2006; Srinivasan *et al.* 2009). At 44 minutes, the difference became negligible probably due to the decrease of light sensitivity and/or influence of study confounders (see 'Study limitations' section). In the only two previous studies on the immediate effect of light on FSH in humans, the moderate or intense bright light increased the concentrations of FSH at night; there was no effect during daytime; and morning light was not used (Miyauchi *et al.* 1990, 1991). As for the non-immediate effect of light on FSH, three reports exist: one documented a significant stimulating effect of morning artificial light on the hormone concentrations in women in follicular phase (Danilenko & Samoilova 2007); in two others, only a slight, if any, stimulating effect on FSH is described (Kripke *et al.* 2010; Grandner *et al.* 2011), however, the study groups were heterogeneous with respect to gender, age and the menstrual cycle phase. In our study, FSH concentrations were measured in mid-to-late follicular phase, and the results corroborate the previous finding that a woman's reproductive system at late follicular phase – compared to other phases of menstrual cycle – is sensitive to light – either artificial (Putilov *et al.* 2002) or natural (Danilenko *et al.* 2011). Studies that investigated Winter-Summer differences in FSH at temperate and high latitudes also revealed higher Summer concentrations when blood was sampled at late follicular phase (Kauppila *et al.* 1987; Danilenko *et al.* 2011), though it was not always the case (Kivelä *et al.* 1988).

The mechanism of the stimulatory action of light on FSH secretion is unknown. The neuronal pathways beginning from the melanopsin-containing ganglion cells in retina synapse several nuclei in hypothalamus, including paraventricular nuclei (LeGates *et al.* 2014). Several hypothalamic nuclei (again, including paraventricular nuclei; Xu *et al.* 2012) produce kisspeptin – a potent activator of gonadotropin releasing hormone (GnRH; Franceschini & Desroziers 2013; Ratnasabapathy & Dhillo 2013) – and two other neuromediators, co-expressed with kisspeptin – neurokinin B and dynorphin (Bartzen-Sprauer *et al.* 2014). The hypothalamic GnRH is released into hypophyseal portal system to activate secretion of LH and FSH. Despite apparent anatomical connections between the melanopsin-containing cells and pituitary cells secreting FSH, the literature lacks studies investigating the immediate functional links within this anatomical circuit in response to light exposure. Though the secretion of both FSH and LH is activated by GnRH, and steady correlations between the changes of FSH and LH were found in our study, the change in LH values in response to white vs. red light did not attain significance. Studies in hamsters indeed suggest that LH and FSH are differentially regulated by the photoperiod (Anand *et al.* 2002), and LH secretion is stimulated by light more slowly (Steger *et al.* 1984).

Other hormones

Likewise LH, secretion of prolactin, estradiol and progesterone were not found to be significantly affected by white vs. red light in our study. We are unaware of any previous studies on the immediate effect of light on progesterone to be compared with our findings. Negative results on estradiol are in line with the previous findings of Graham *et al.* (2001). In the studies which investigated immediate effect of light on LH concentrations (see Introduction), in one LH values were also unchanged (Miyauchi *et al.* 1991), in another – increased (Miyauchi *et al.* 1990). The immediate effect of light on prolactin was more extensively studied, but the findings are contradictory (see Introduction).

Cortisol concentrations in our study did not change differently either. Studies allowing immediate estimate – within the first 30–45 minutes – of cortisol response to light presenting via open eyes, showed a (temporal) increase (Scheer & Buijs 1999; Leproult *et al.* 2001; Figueiro & Rea 2012) or no change (Petterborg *et al.* 1991; Leproult *et al.* 1997; Rüger *et al.* 2006; Jung *et al.* 2010) at night/morning. Some studies explored wavelength-specific light. One did not find a difference between the 460-nm and 555-nm monochromatic lights presented for 6.5 hours, in their effects on cortisol concentrations (Lockley *et al.* 2006); the limitation of the study, however, was a use of between-subject design. In another study, light not filtered from the blue portion and presented from 20:00 to 08:00, profoundly increased cortisol values at 02:00 and 04:00 but not at 22:00, 24:00, 06:00 or 08:00 (Rahman *et al.* 2011). In the third study, blue light presented for 80 minutes from 06:00, increased post-awakening cortisol values (Figueiro & Rea 2012). A time from the cortisol awakening response (CAR, a sharp temporal increase for 30–45 minutes Caufriez *et al.* 2009; Clow *et al.* 2010) to the first blood sampling was not controlled in our study which might confound the cortisol results. Nevertheless, cortisol data indicated no stress reactions to any light session, an important control measurement in our study.

Study limitations

The major limitation of this study was allowing only 5 minutes average time seated before the initial blood and saliva sampling whereas the posture-related change of concentration of hormones (due to the shifts of 10–20% of fluid from interstitial to intravascular space) lasts 20 minutes (Hagan *et al.* 1978; Deacon & Arendt 1994). Therefore, the value at the 20th minute of light exposure could not be a reliable reference to the next, third time point measurement. Another limitation includes uneven proportion of white-red and red-white light sessions sequence (10:6) especially in the light of finding that some hormonal values significantly varied even within 2–3 days in the mid-follicular phase of the menstrual cycle. Knowing now that the effect of light on reproductive hormones may be much milder than on melatonin, the ideal design would be to start the study at post-sleep rest/darkness; more frequent (every 10–15 minutes) sampling; shorter (1 day) inter-session interval; and probably brighter white light. One more limitation includes possible masking of LH, FSH and estradiol results by pulsatile secretion of these hormones (Pincus *et al.* 1997; Caufriez *et al.* 2009). Whereas the hormonal analysis was indeed adjusted for time seated and the session sequence, the influence of pulsatility on the hormonal results could not be statistically ruled out.

In summary, our study adds to the body of evidence that suggests light is not a vestigial factor driving the reproductive system in humans, and sheds some light on a possible central mechanism of its action.

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