

DAYLIGHTING (4.430)

MIT Architecture

Circadian photoreception in humans: More than meets the eye

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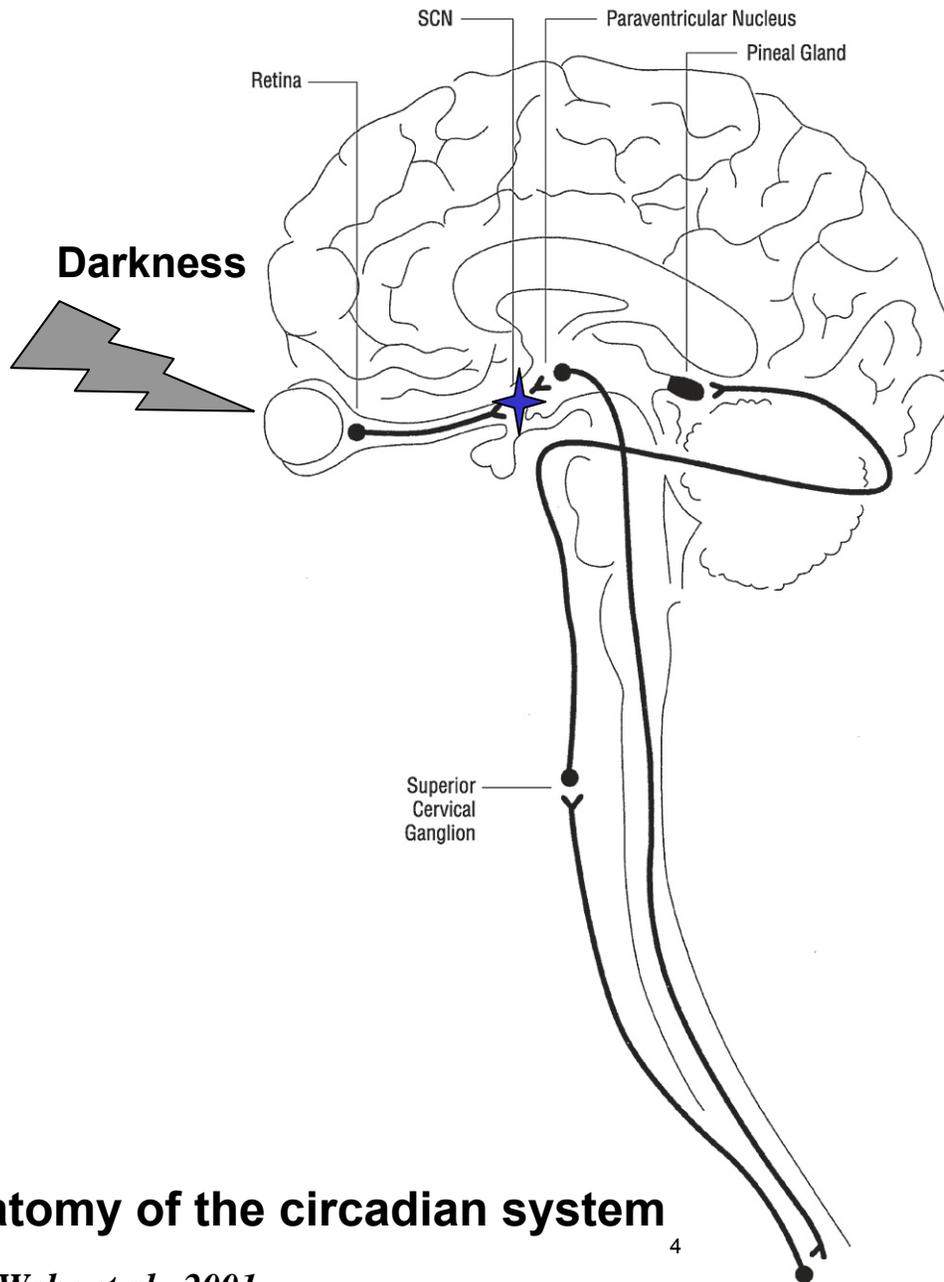
Division of Sleep Medicine, Harvard Medical School, Boston, MA

The ‘body clock’ or circadian pacemaker is situated in suprachiasmatic nucleus (SCN) of hypothalamus

It controls the timing of most 24-hour behavioral and physiological rhythms including the sleep-wake cycle, alertness and performance rhythms, hormone production, temperature regulation, and metabolism.

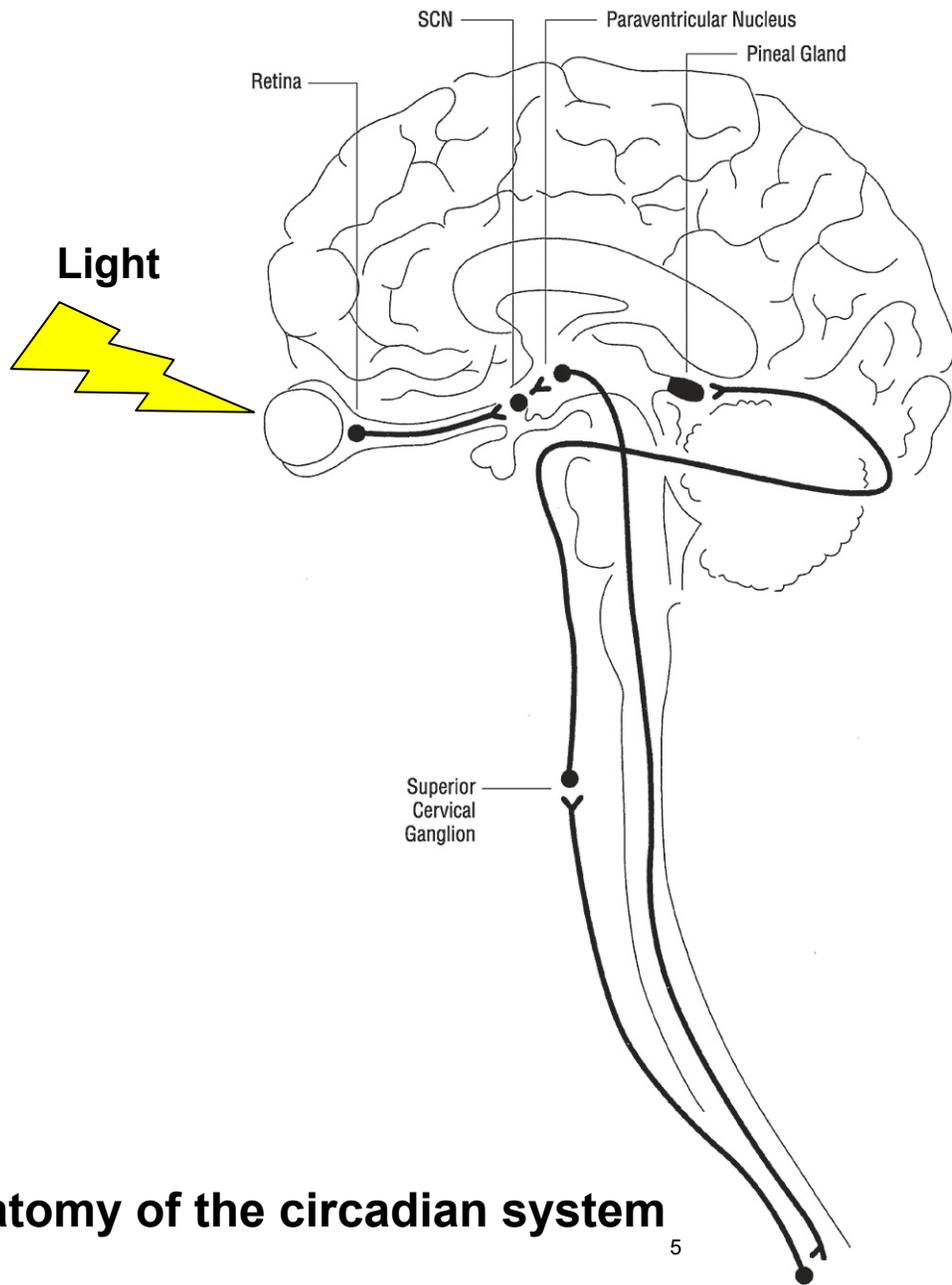
Period of the circadian pacemaker in humans

- Average ~24.2 h (23.6-25.0 h)
- Stable in healthy aging
- Determines direction and extent of daily shift required to entrain to 24 h
 - phase angle of entrainment
 - diurnal preference or 'owl vs lark'
 - adaptation to jet-lag or shiftwork
- Genetic basis



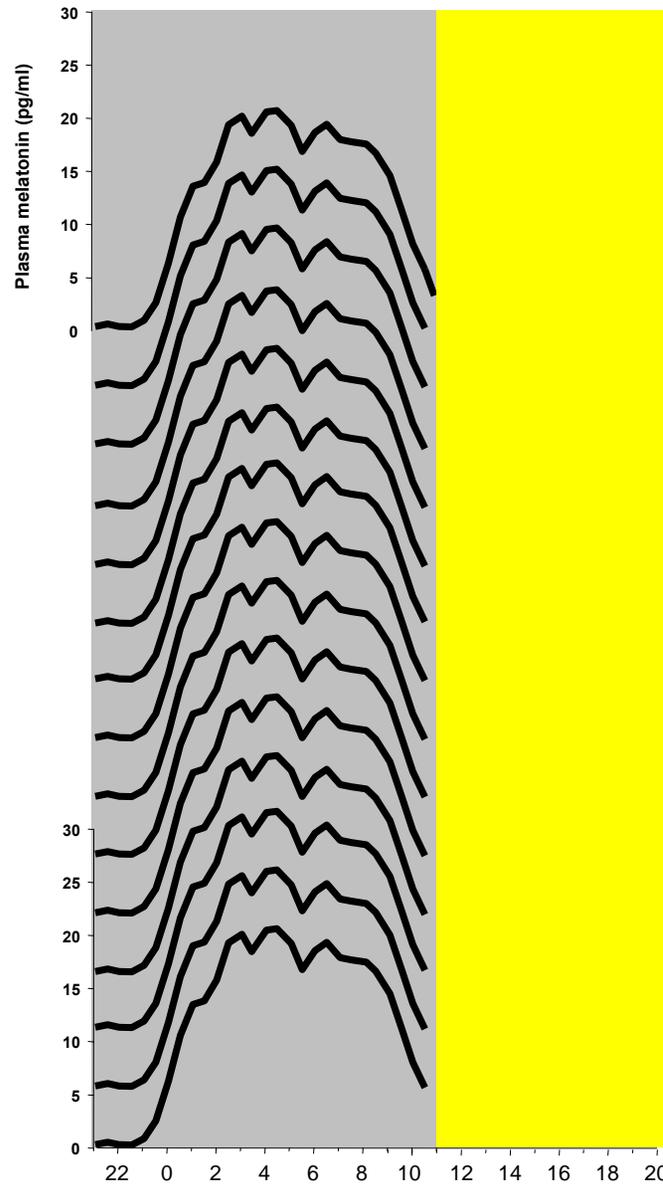
Neuroanatomy of the circadian system

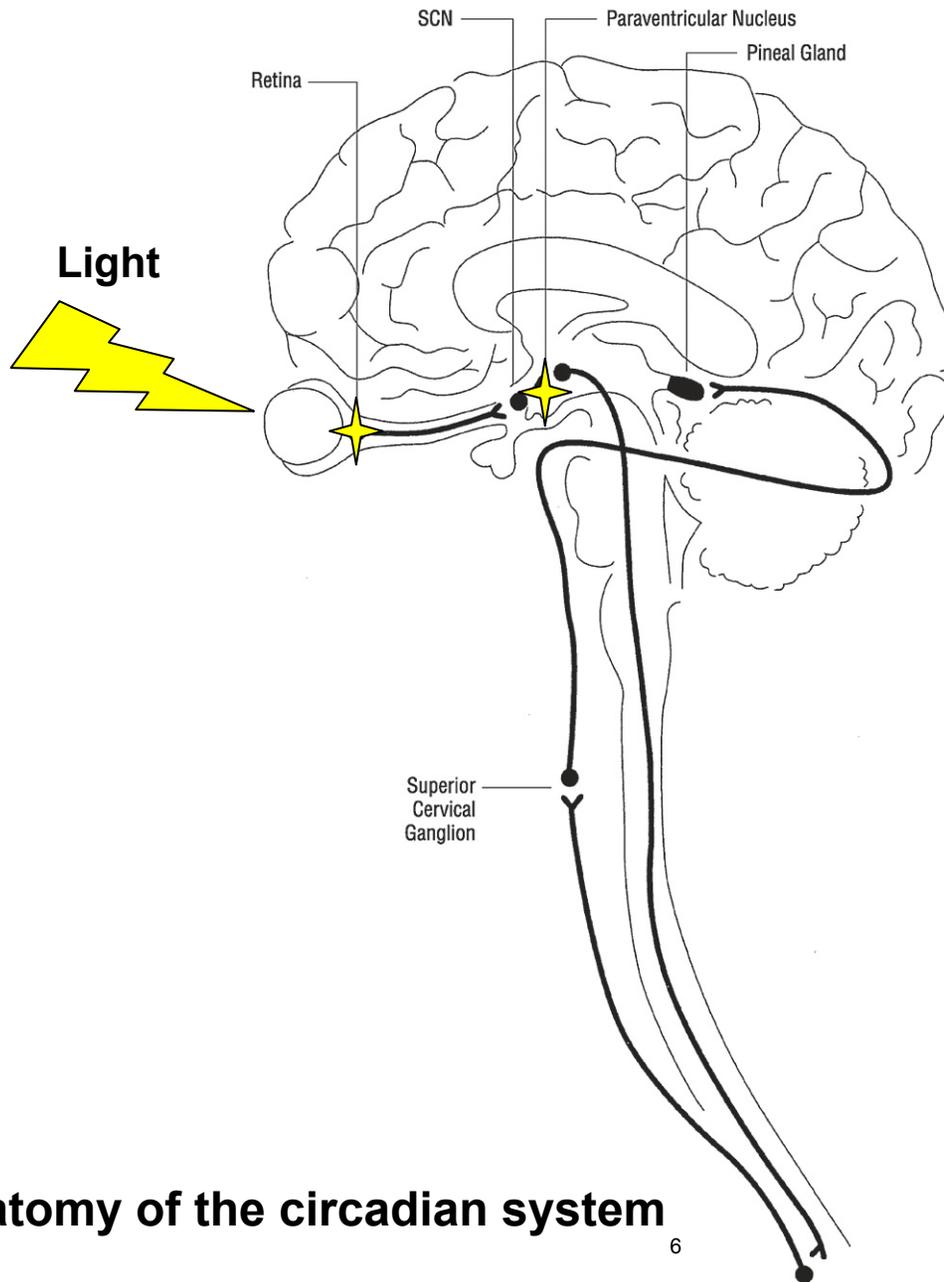
Adapted from Wehr et al., 2001



Neuroanatomy of the circadian system

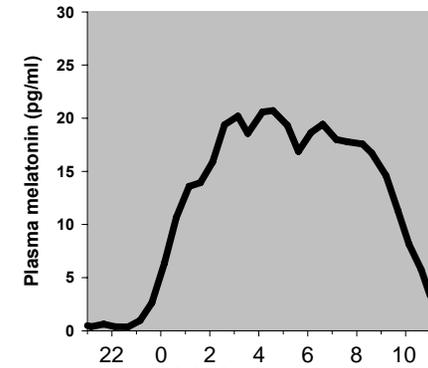
Pineal melatonin response
Entrainment by light



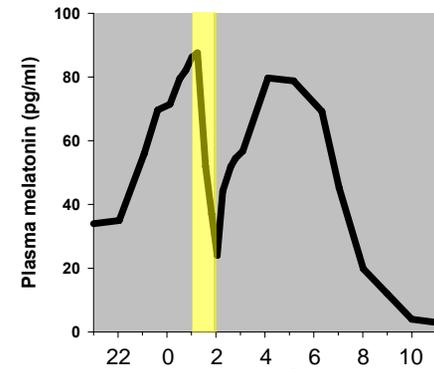


Pineal melatonin response

Continuous darkness



Light pulse



Neuroanatomy of the circadian system

‘Non-Visual’ Photoreception

Multiple neuroendocrine and neurobehavioral responses

- Light is the most powerful time cue for resetting the circadian pacemaker and ensuring correct synchronization of the internal clock with the environment
- Failure to entrain the circadian pacemaker results in sleep disorders, fatigue, performance problems, hormone and metabolic disorders
- Common examples include the circadian desynchronization caused by shift-work, jet-lag and Advanced- and Delayed Sleep Phase Disorder

‘Non-Visual’ Photoreception

Multiple neuroendocrine and neurobehavioral responses

- Much like the ear has dual functions for audition and balance, the human eye has a dual role in detecting light for a range of behavioral and physiological responses separate and apart from sight
- These ‘non-visual’ effects of light are mediated by a novel non-rod, non-cone photoreceptor located in the ganglion cell layer of the eye
- These photosensitive ganglion cells contain a novel opsin, melanopsin, to detect light which is maximally sensitive to short-wavelength (blue) visible light ($\lambda_{\max} \sim 480 \text{ nm}$)

‘Non-Visual’ Photoreception

Multiple neuroendocrine and neurobehavioral responses

- **Circadian entrainment**
- **Circadian phase shifting**

- **Melatonin suppression**
- **Subjective alertness / EEG**
- **Neurobehavioral performance**
- **Cortisol stimulation**
- **Cardio- and thermoregulation**
- **Pupillary reflex**
- **Stimulation of clock gene expression**

- **Photoperiodism and seasonality**
- **Solar navigation**

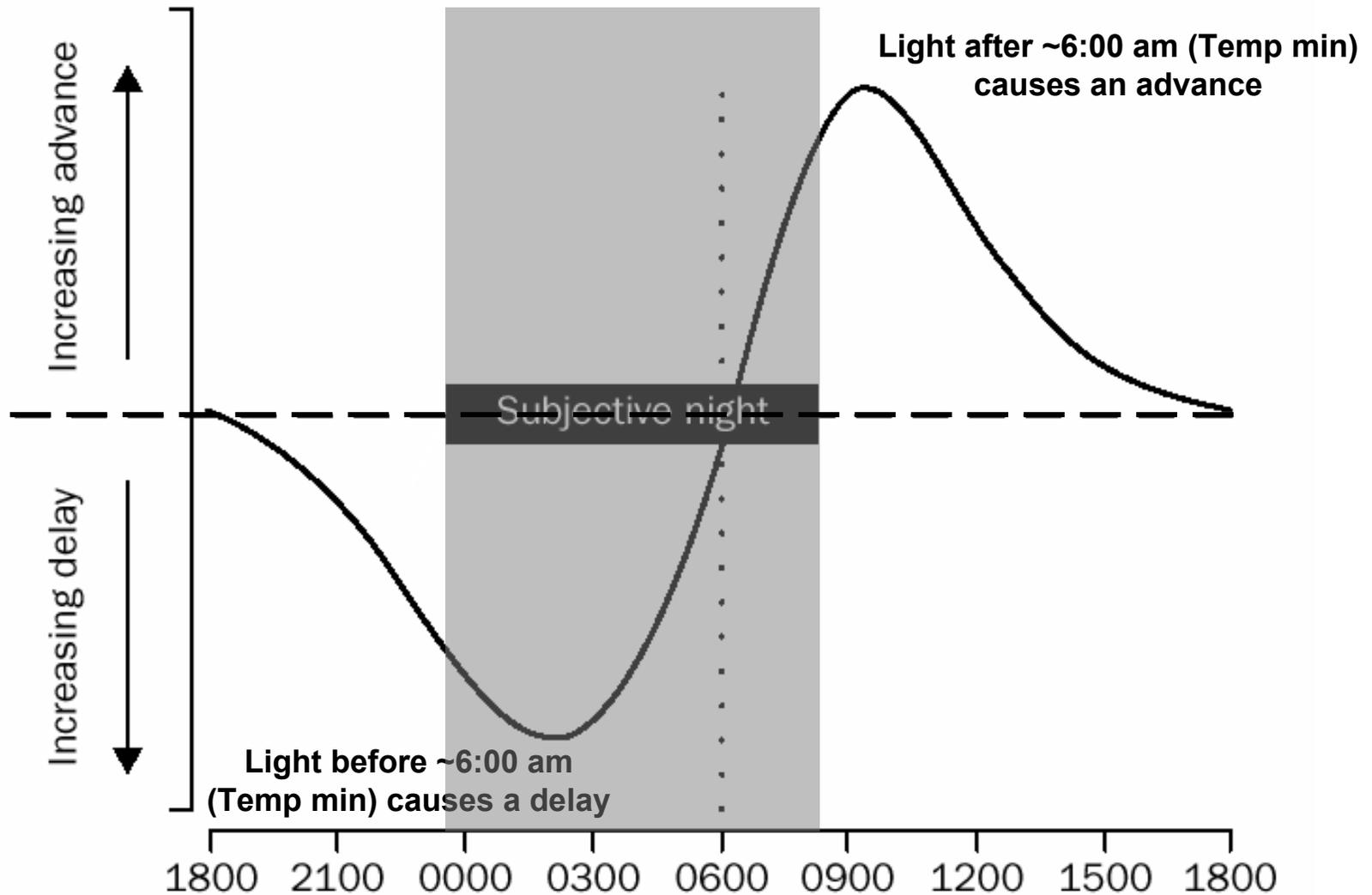
‘Non-Visual’ Photoreception

Properties of light affecting circadian photoreception

- **Intensity**
- **Timing**
- **Pattern**
- **Light history**
- **Wavelength**

Phase-shifting effects of light exposure are time-dependent

Magnitude and direction of shift is described by a Phase Response Curve (PRC)



Phase-shifting effects of light pattern exhibit a non-linear relationship

Shorter-duration exposures cause relatively stronger effects

**23% of intermittent light exposure provides
74% of the continuous light response**

*Rimmer et al., Am J Physiol 2000
Gronfier et al. Am J Physiol 2004*

Melatonin suppressive effects of light depend on prior light exposure

Prior exposure to bright light reduces the subsequent light response

**Melatonin suppression reduced by ~15%
after pre-exposure to 200 lux (71%) as compared to pre-exposure to ~0.5 lux (86%)**

‘Non-Visual’ Photoreception

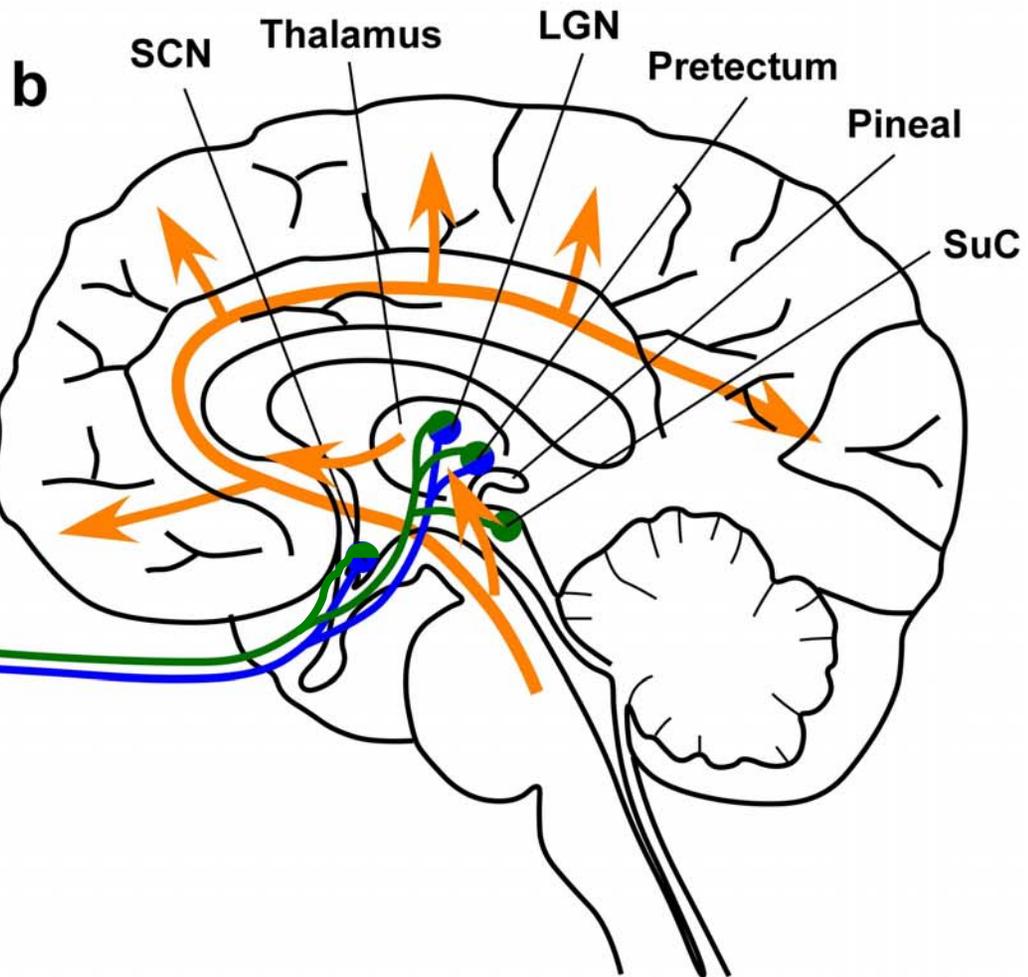
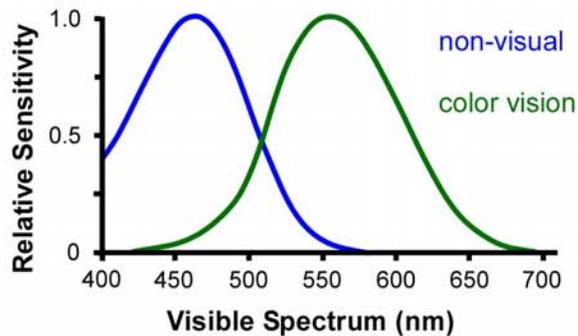
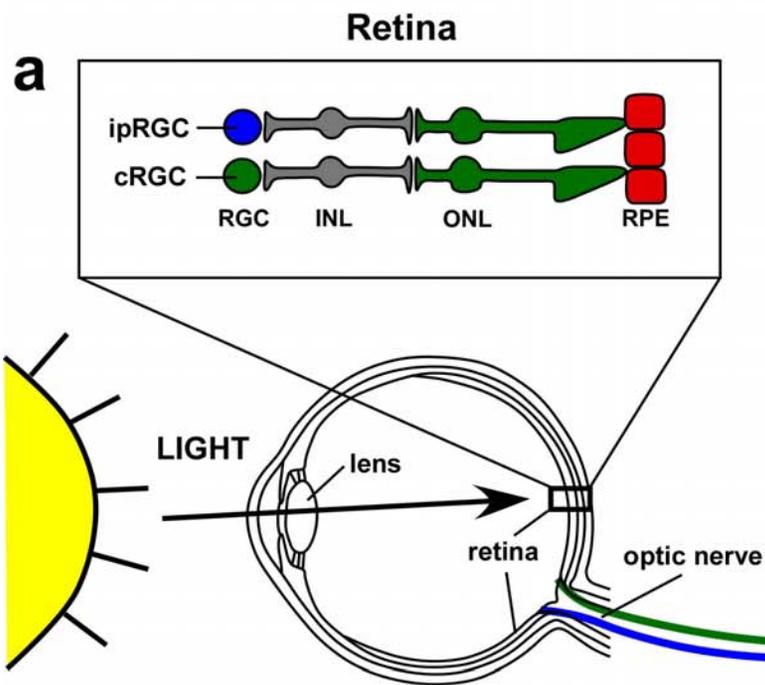
Properties of light affecting circadian photoreception

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‘Non-Visual’ Photoreception

What is the evidence for a novel photoreceptor system?

- Some totally visually blind people with eyes maintain normal melatonin suppression response to light and have normal circadian entrainment
- Color vision-deficient people maintain normal melatonin suppression to white and green light
- The spectral sensitivity of ‘non-visual’ responses to light is blue-shifted relative to the photopic or scotopic visual systems and does not match the spectral sensitivity of rod or cone photoreceptors



Summary - Neurobiology

‘Non-visual’ photoreception in humans

- requires eyes
- minimal light perception is sufficient
- not associated with visual field loss
- functional cones and /or rods not required
- short-wavelength blue-light sensitivity at high intensity
- adaptive multi-photoreceptor system
- responses are light wavelength-, intensity, duration- and history-dependent
- *same for day-time exposures?*
- *same for all ‘non-image forming’ responses?*
- photopic lux is an inadequate measure for the non-visual response to light

Light Applications - Clinical

- **Treatment of circadian rhythm sleep disorders**
 - Advanced-, Delayed-, Non-24-hour Sleep Disorders
 - Shift-work Disorder, Jet-lag
 - Sleep timing changes due to adolescence and aging
- **Entrainment to non-24-hour 'days'**
 - Space flight and bases, Submariners, Antarctica
- **Treatment of affective disorders**
 - Seasonal Affective Disorder (*Glickman et al., 2005; Anderson et al., 2009*)
 - Dementia (*Riemersma-van der Lek et al., JAMA 2008*)
 - General mood, non-seasonal depression?
- **Improving sleep patterns in clinical groups**
 - Hospital patients
 - Care home patients
 - Psychiatric inpatients
 - Child and adolescent sleep

General criteria for Circadian Rhythm Sleep Disorder

International Classification of Sleep Disorders II

- Jet-lag type
- Shift work type
- Delayed sleep phase type (DSPS)
- Advanced sleep phase type (ASPS)
- Non-entrained type (e.g. blind)

- Irregular sleep-wake type
- Medical condition-related
- Drug or substance-related
- Non-specific

Rapid transmeridian travel induces jet-lag

- **Insomnia or excessive sleepiness following travel across ≥ 2 time zones**
- **Internal circadian system cannot keep up with rapid light-dark change**
- **Readjusts at a slow rate ($\sim 1\text{h/day}$) causing chronic desynchronisation**
- **Social and behavioural factors greatly influence readaptation rates**
- **More severe during eastward travel for majority of population**
- **Symptoms include**
 - **insomnia**
 - **fatigue**
 - **GIT disorders**
 - **poor performance, memory and concentration**

**Circadian period is close to but not exactly 24 h
and needs to be reset to 24 h every day**

75% naturally delay ('westward')

- require phase advance to entrain each day

25% naturally advance ('eastward')

- require phase delay to entrain each day

To remember the required direction of shift to adapt, think about what people are doing right now at the destination

Westward travel requires a phase delay shift

**People in LA (3 h westward) are still asleep
They will wake up 'later' than you in absolute time
Their behaviors are DELAYED relative to you
You need to DELAY your clock to adapt to LA**

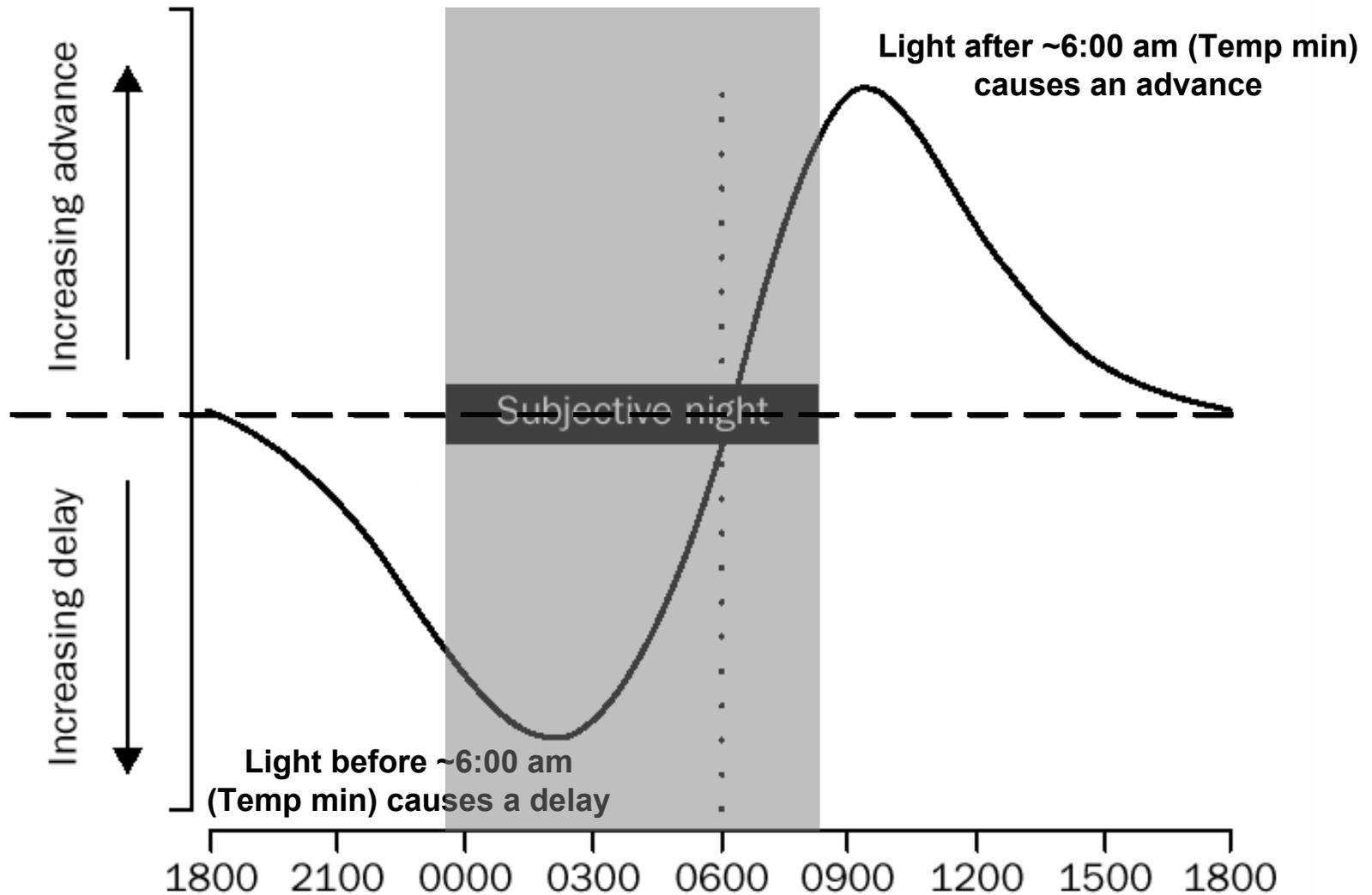
Eastward travel requires a phase advance shift

**People in London (5 h eastward) are having lunch
They are eating lunch 'earlier' than you in absolute time
Their behaviors are ADVANCED relative to you
You need to ADVANCE your clock to adapt to London**

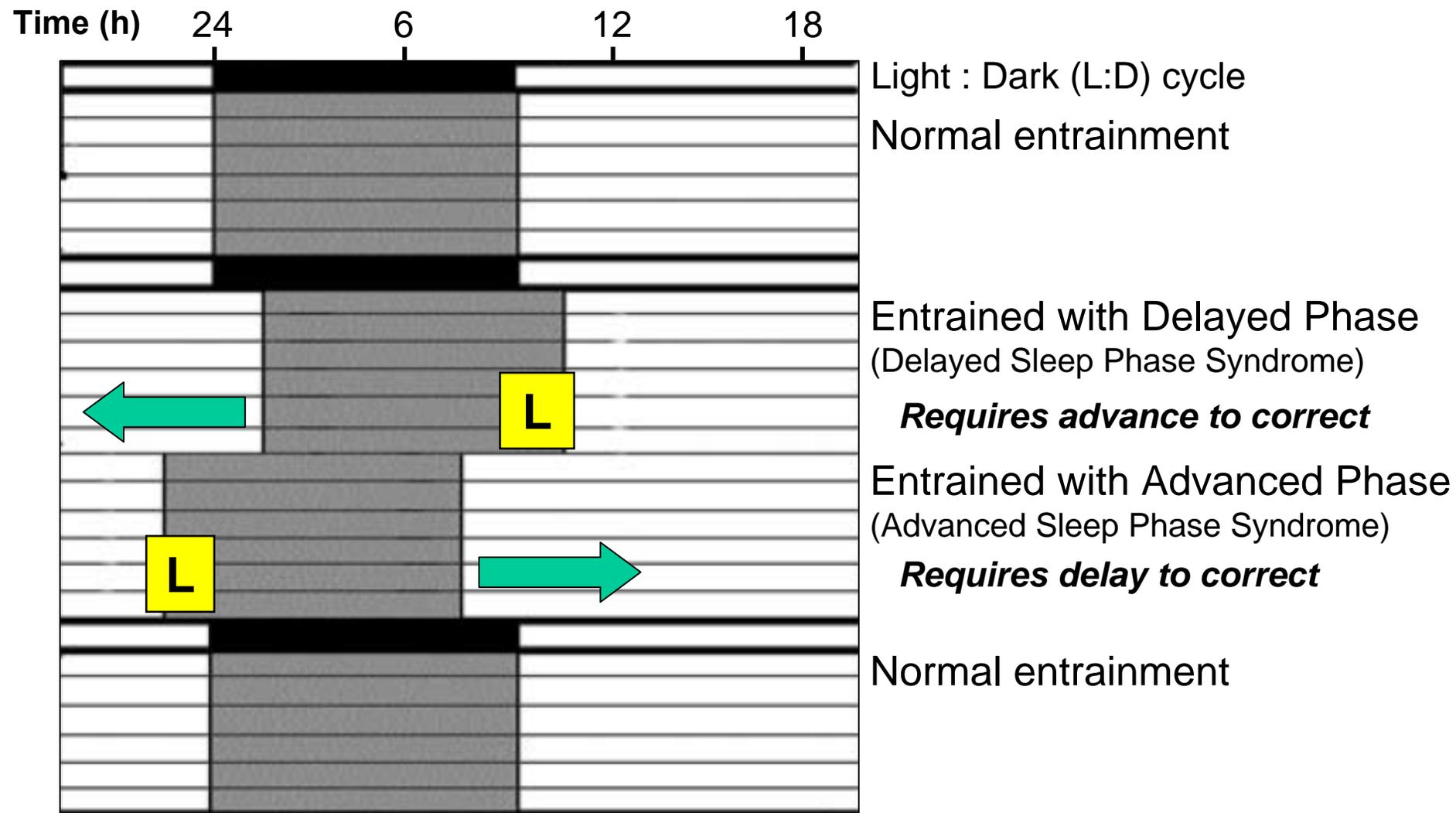
Note: 5 h eastward = 19 h westward

Phase-shifting effects of light exposure are time-dependent

Magnitude and direction of shift is described by a Phase Response Curve (PRC)



Schematic of timing for light treatment of Circadian Rhythm Sleep Disorders



Light exposure **AT NIGHT** stimulates multiple circadian, hormonal and behavioral responses in humans

- Phase-shifting the timing of the circadian pacemaker
 - ↳ **DESYNCHRONIZES INTERNAL CIRCADIAN RHYTHMS AND DISRUPTS SLEEP AND HORMONE SIGNALS**
- Suppression of pineal hormone melatonin at night
 - ↳ **ABOLISHES BIOCHEMICAL SIGNAL OF DARKNESS**
- Enhancement of alertness and neurobehavioral performance
 - ↳ **ALERTS THE BRAIN AND DISRUPTS SLEEP**
- Increase in heart rate and temperature at night
 - ↳ **WIDESPREAD IMPACT ON PHYSIOLOGY, METABOLISM, AND GENE EXPRESSION BRAIN- AND BODY-WIDE**

Consequences of shift work disorder or short sleep

Circadian misalignment and sleep disruption likely underlie increased risk of accidents and injuries, heart disease, metabolic disorders and diabetes and some cancers in shift-workers

‘shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2A)’

WHO International Agency for Research on Cancer Monograph Working Group

Straif et al., Lancet Oncol 8, 2007

Short sleep duration in non-shift-working populations is associated with increased risk of hypertension, stroke and heart attack, obesity, Type II diabetes and possibly mortality

Circadian oscillators in liver, heart, lung, ovaries, stomach, esophagus, kidneys, bladder.....etc, etc

Light Applications - Clinical

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 - General mood, non-seasonal depression?
- **Improving general sleep patterns**
 - Hospital and institutionalized patients
 - Child and adolescent sleep

Light Applications - General

- **Non-pharmacological sleepiness countermeasure**
- **Safe, reversible, short-acting, inexpensive**
- **High levels of caffeine use illustrate need**
 - Offices, schools, colleges, factories, control rooms...
 - Military, security, transport (pilots, captains, truck/car/train drivers)
 - Safety-sensitive occupations (physicians, nurses, nuclear...)
 - Anywhere where enhanced alertness and safety is important
- **Challenge is to incorporate these benefits into design**
- **Lighting design to optimize visual and non-visual effects**
- **Flexible, 'smart' lighting systems with user interaction**

Modeling 'circadian efficacy' and architectural design for lighting

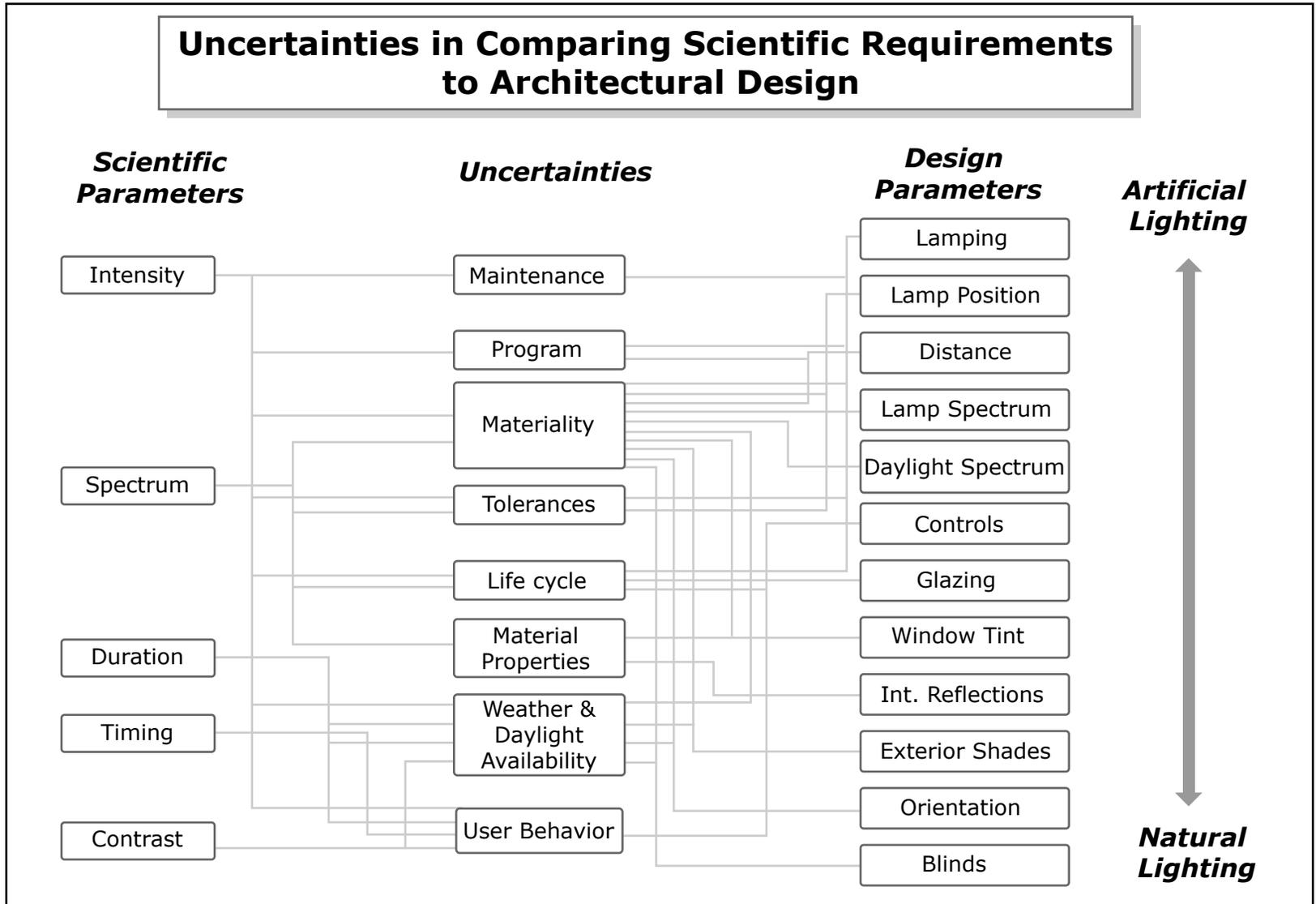


Image by MIT OpenCourseWare. Source: Fig. 3 in Pechacek, C. S., M. Andersen, and S. W. Lockley. "Preliminary method for prospective analysis of the circadian efficacy of (Day)light with applications to healthcare architecture." *LEUKOS: The Journal of the Illuminating Engineering Society of North America* 5, no. 1 (2008): 1-26.

Key Questions

- **How do we incorporate these findings in real-world applications?**
- **How do lighting designers model the dual effects of light?**
- **What more information do designers need?**
- **How to approach ‘smart lighting’?**
- **Energy considerations?**
- **Safety considerations?**
- **Light pollution, role of darkness?**

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