Light, body clocks and sleep - SE13

Friday 4th January 2013
10:15 - 11:00
Location: Palmer, 109

Russell G. Foster FRS
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Head, Nuffield Laboratory of Ophthalmology
Fellow, Brasenose College
E-mail: russell.foster@eye.ox.ac.uk
• Introduction – The Body Clock
• Light Regulation of The Body Clock
• Time of Day Effects
• Disruption of the Body Clock
• Discussion
• Introduction – The Body Clock
• Light Regulation of The Body Clock
• Time of Day Effects
• Disruption of the Body Clock
• Discussion
24h body clocks (circadian clocks) and sleep processes have captured the popular imagination……
Sometimes... not always helpful!
Time to set your body clock

6AM HAVE SEX
It's good news for early birds. "Sex hormones build up overnight, so this is the optimum time to have sex as oestrogen and testosterone levels are at their peak," says Professor Jim Horner, Director of the Sleep Research Centre at Loughborough University. "Sleeping women have the least desire for sex, whereas women just waking up are at their highest level."

7.30AM MOISTURISE YOUR SKIN
Skin feels dehydrated overnight, so moisturise your body in the morning, preferably after a bath or shower when open pores increase absorption.

8AM POP A PILL
Research has shown that women who take the contraceptive pill in the morning are 10 times less likely to forget it.

8.30AM TAKE YOUR VITAMINS
The digestive system works at its peak early in the morning, so try taking your vitamins now.

10AM HAVE A BIKINI WAX
If you're having a waxing, it's best to do it in the mornings. It's less painful and easier to manage. The area can be rinsed and dried, and there's not enough time for the hair to grow back.

12NOON GIVE A PRESENTATION
Increased adrenaline levels help you deal with stress, so if you're giving a talk or presentation, this is the perfect time to do it. The energy levels are high and the audience is interested.

1PM HAVE LUNCH
Don't be tempted by a late lunch. People buy more high-calorie food between 1 and 5pm because they've missed their body's natural eating time of 1pm.

1.30PM USE YOUR LOAF
Lozenges, mints, sweets and short-term memory are at their best at this time, so now's the time to concentrate, memorise or commit something to memory. The brain is at its sharpest,

2.30PM TAKE IT EASY
Take two minutes to de-stress and to take stock of your day. A "meditation minute" can help you relax and focus, and if you're out shopping, take a few minutes to relax and refocus.

5PM EXERCISE
This is the ideal time for vigorous exercise. As well as speeding up reaction times, your hand-eye co-ordination is also at its best and body temperature, muscle strength and overall flexibility peak, making you less prone to injury. Exercise during late afternoon, which will help to increase energy.

6PM HAVE A TREAT
YOUR sense of smell, taste and hearing are most acute around now, so it's the ideal time to enjoy the best food you've prepared, or a toast of your favourite music.

7PM TAKE AN EVENING CLASS
"THREE hours we get our second wave of alertness and productivity," says Professor Jim Horner. "Our ability to reason and perform complex tasks is almost as good now as during the morning, so it's an excellent time to do an evening class.

8PM HAVE A DRINK
ENZYMEs in the liver responsible for breaking down alcohol are at their most effective around now. Make sure you've eaten from the nibbles by 8pm though, as your body's ability to absorb alcohol drops dramatically after that.

9.30PM HAVE SEX (AGAIN)
Skin is at its most sensitive at this time, so if you go through your fave CRM e-mail or if you don't - now is the perfect time to catch up on your e-mails.

10PM GO TO SLEEP
Research by the Body Rhythms Centre found that people who go to bed at 10pm are more alert the following day. "Your body temperature starts to fall and heart rate slows, preparing the body for sleep," says Professor Horner.
Time to set your body clock

**8AM** Have Sex
It’s good news for early birds. “Sex hormones build up overnight, so this is the optimum time to have sex,” an endocrinologist and biochemist from the University of Oxford, UK, told us. His advice: “Have a healthy breakfast and enjoy sex.”

**7.30AM** Moisturise Your Skin
This is when your skin is most receptive to moisturiser. However, if you’re in a rush, you can use a gentle cleanser and then apply a light moisturiser.

**8AM** Pop a Pill
Research has shown that women who take the morning-after pill at the crack of dawn are 10 times less likely to get pregnant.

**8.30AM** Take Your Vitamins
The digestive system works at its peak early in the morning, so by taking your vitamins now, you’ll be better equipped to absorb nutrients throughout the day.

**10AM** Have a Bikini Wax
Off an injection, or a visit to the dentist – basically anything with an “ouch!” Sound off between 8 and 9am,” says Professor Russell Foster, co-author of the book “Sleeping with Your Eyes Wide Open.”

**12.00PM** Give A Presentation
Increased adrenaline levels help you deal with stressful situations. It’s also a great time to eat lunch, as your body will have had time to digest breakfast and your filled up with energising nutrients.

**1.00PM** Don’t Eat Lunch
People buy more high-fat, high-salt food between 1 and 2pm because they’re rushed. They need a healthy lunch to keep their energy levels up and their minds sharp.

**1.30PM** Use Your Loaf
Logical reasoning, alertness and short-term memory are at their best at this time, so make the most of it by concentrating, negotiating or communicating. “People are at their creative best in the afternoon, especially if they’re in a good mood,” says Professor Foster.

**2.30PM** Take It Easy
There’s a drop in our ability to perform complex and mind-intensive tasks come the afternoon, regardless of whether we’ve had anything to eat or drink.

**3PM** Have a Nap
Mid-afternoon is the perfect time for a snooze. “Research indicates that if you have a long sleep at night and a short nap in the afternoon,” says Professor Jim Horne, Director of the Sleep Research Centre at Loughborough University. “Spending 15 to 20 minutes napping will aid your health. Between 15 and 45 minutes is the optimum rest period.

**4PM** Make a Complaint
Reactions are faster in the afternoon, which may just make you quicker with salesmen at the supermarket.

**5PM** Exercise
This is the ideal time for vigorous exercise. As well as a speedy reaction time, your hand-eye coordination is also at its best and body temperature, muscle strength and overall flexibility peak, making you less prone to injury when you exercise during late afternoon, which will help to increase energy.

**6PM** Have A Treat
Your senses of smell, taste and hearing are most acute around dusk, so it’s the ideal time to enjoy a glass of wine or a plate of your favourite food.

**9.30PM** Sex (Again)
The quality and quantity of sex are at their peak around 9.30pm, according to Professor Foster. “It’s 35 per cent higher than the norm,” he says. “And if you’re still awake, prepare the body for sleep,” says Professor Foster.

**10PM** Go to Bed
“Bed at 10pm and you’ll feel well rested,” says Professor Foster. “And you’ll have energy for the next morning.”

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**NATURAL RHYTHMS RULE, OUR BODIES AND DICTATE THE BEST TIMES FOR A RANGE OF ACTIVITIES. HERE’S OUR COUNTDOWN...**

By Beth Gibbon
10AM HAVE A BIKINI WAX

OR an injection, or a visit to the dentist — basically, anything with an “ouch” factor. “Pain intensity is at its lowest between 8 and 10am,” says Professor Russell Foster, co-author of Rhythms of Life (Profile Books, £9.99). “It’s not entirely clear why, but it’s probably because pain receptors aren’t as alert as they are later in the day.”

THAT'S WHY:

• DO something plucking your eye, this is when we:
  • HAVE a big meal
  • START a car journey

Mental performance
Time to set your body clock

6AM HAVE SEX
It's good news for earlybirds. "Sex hormones build up overnight, so this is the optimum time to have sex as oestrogen and testosterone levels are at their highest," says Dr. Philip Lee, author of The Lazy Girls Guide To Good Sex (Plum Press 1999).

7.30AM MOISTURISE YOUR SKIN
Skin feels dehydrated overnight, so moisturise your body in the morning, preferably after a bath or shower when skin pores are more open.

8AM POP A PILL
Research has shown that women who take the contraceptive pill in the morning are 10 times less likely to forget it.

8.30AM TAKE YOUR VITAMINS
The digestive system works at its peak early in the morning, so try eating your vitamins now.

10AM HAVE A BIKINI WAX
Or an injection, or a visit to the dentist – basically anything with an "ouch!" factor works best between 8 and 10am," says Professor Russell Foster, co-author of Blips and Bleeps: How Your Body Works on a 24-Hour Clock (Penguin 2001), which, he says, is "an entirely clear cut off point. Pain receptors aren’t as alert so they are in the day.

12NOON GIVE A PRESENTATION
Presentation skills are at their highest levels help you deal with stress. Brains, which are used a lot now, will also sound its best around noon.

1PM HAVE LUNCH
Don't be tempted by a late lunch. People buy more high-fat, sugary food between 1 and 2pm because they've missed their body's natural eating pattern.

1.30PM USE YOUR LOAF
Logically, memory, alertness and short-term memory are at their best at this time, so now's the time to concentrate, memorise or commit something to memory.

2.30PM TAKE IT EASY
The time to QUIT is drop in our ability to perform. Numerical and mental arithmetic tasks come the afternoon, regardless of whether we've had anything to eat or drink... says Professor Foster, but we make more mistakes because our mind is at its sharpest," says Professor Foster.

2.30PM MAKE A COMPLAINT
Reaction times are faster in the afternoon, which may just make you quicker with killer comments at the customer service desk.

3PM EXERCISE
This is the ideal time for vigorous exercise. As well as speeding reaction times, your hand-eye coordination is also at its best and body temperature, muscle strength and overall flexibility peak, making you less prone to injury.

3PM HAVE A NAP
Mid-afternoon is the perfect time for a snooze. "Women are designed to have a long sleep at night and a shorter nap in the afternoon," says Professor Jim Horne, Director of the Sleep Research Centre at Loughborough University. Sleep researchers at Loughborough have found that women are much better with sleep, and even introducing weekend naps would boost their health. Between 30 and 40 minutes is the optimum afternoon siesta.

4PM MAKE A COMPLAINT
REACTION times are faster in the afternoon, which may just make you quicker with killer comments at the customer services desk.

5PM EXERCISE
This is the ideal time for vigorous exercise. As well as speeding reaction times, your hand-eye coordination is also at its best and body temperature, muscle strength and overall flexibility peak, making you less prone to injury.

5PM MAKE BABIES
The quality and quantity of your sex life during this time is 30% greater than the morning. Women are much more likely to ovulate between 5pm and 8pm, making it the perfect time for baby making.

5.30pm HERALDS THE START OF TWO AND A HALF HOURS OF SEX AND BOOZE

6PM HAVE A TREAT
Your sense of smell, taste and hearing are most acute around now, so it is the ideal time to eat good food, or a blast of your favourite music.

6.30PM MAKE BABIES
The quality and quantity of your sex life during this time is 30% greater than the morning. Women are much more likely to ovulate between 5pm and 8pm, making it the perfect time for baby making.

6.30pm HERALDS THE START OF TWO AND A HALF HOURS OF SEX AND BOOZE

8PM HAVE A TREAT
Your sense of smell, taste and hearing are most acute around now, so it is the ideal time to eat good food, or a blast of your favourite music.

9.30PM MAKE BABIES
The quality and quantity of your sex life during this time is 30% greater than the morning. Women are much more likely to ovulate between 5pm and 8pm, making it the perfect time for baby making.

10PM GO TO SLEEP
Research by the Body Rhythm Centre found that people who go to bed at 10pm are more alert the following day. "Your body temperature starts to drop at 10pm, so going to bed at this time is the perfect time to catch up on zzz's."

Skin is at its most sensitive at this time, so if you sleep through your alarm clock – it’s even if you don’t – now is the perfect time to catch up on zzz's.
### Rhythmic Changes in Human Physiology and Behaviour

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#### Base-line Changes

- **A**: Plasma melatonin concentration (μg/mL)
- **B**: Core body temperature (°C)
- **C**: Subjective alertness (0 = not alert, 100 = very alert)
- **D**: Task performance reaction time (sec)
- **E**: Triglyceride concentration (mmol/L)
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Our biology is highly dynamic and "fine-tunes" physiology and behaviour to the varying demands of activity and rest.
The Circadian System

Suprachiasmatic Nuclei (SCN)
The Circadian System

SCN

Suprachiasmatic Nuclei
The Circadian System

Suprachiasmatic Nuclei

Rhythmic 24h

Actogram
The Circadian System

SCN

Suprachiasmatic Nuclei

Arrhythmic Non-24h
The Circadian System

The clock must be the product of subcellular processes!

SCN

Suprachiasmatic Nuclei
Genome Analysis - the basic building blocks of the molecular clock are conserved between all animals!
Molecular Feedback Loop
Molecular Feedback Loop

CRY 1-2

Promoter

Clock

Bmal1

Cry 1-2

CRY

PER

CRY

PER

Cry 1-2

Promoter

Per 1-3

Promoter

CRY

PER

PER
Molecular Feedback Loop

Clock
Promoter
Bmal1
Cry 1-2

PER
CRY

Clock
Promoter
Bmal1
Per 1-3

CRY

PER
Circadian rhythms don’t just involve the SCN
The Circadian System

SCN

Suprachiasmatic Nuclei
Changes in clock genes are being linked to particular “morning” and “evening” sleep types.
Perhaps the best example so far:
Familial Advanced Sleep Phase Syndrome (FASPS)

Grandmother, Daughter, Granddaughter:

K. J. Reid et al., Archives of Neurology 58 (2001)
Familial Advanced Sleep Phase Syndrome (FASPS)

Grandmother, Daughter, Granddaughter:

Fall Asleep ~ 19:30
Wake ~ 03:30

K. J. Reid et al., Archives of Neurology 58 (2001)
Molecular Feedback Loop

Cry 1-2
Promoter

Clock
Bmal1

Per 1-3
Promoter

CRY
PER

CRY
PER
Not just genes that drive “morning” and “evening” types – hormones too!
Morning vs Evening Preference changes with age

Roenneberg *et al.*, Curr Biol, 2004
Morning vs Evening Preference changes with age

Roenneberg et al., Curr Biol, 2004
Introduction – The Body Clock

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Disruption of the Body Clock

Discussion
The Circadian System

Eye

Suprachiasmatic Nuclei (SCN)
The Circadian System

Eye → SCN → Freerunning

Suprachiasmatic Nuclei
How Does The Eye Regulate Internal Time?

- Rods and Cones
- Horizontal cell
- Bipolar cell
- Amacrine cell
- Retinal ganglion cell
- Optic nerve
1st Approach Mutant “blind” mice e.g. $rd/rd$ or $rds$


Visually blind mice
Wheel Running Behaviour

Entrainment

Freerunning

$\Delta \phi$
The Circadian System

Normal Circadian Responses to Light!

Irradiance (log µW cm²)
A Mouse can be visually blind but not circadian blind!

Could there be an uncharacterized photoreceptor within the eye – different from the rods and cones?
Vision Neuroscientists

NO!

NO!

NO!

NO!

Ha Ha Ha!
One semi-reasonable criticism was....

“The circadian system can probably maintain normal photosensitivity with reduced numbers of rods and/or cones?”
Transgenic Rodless + Coneless Mouse (rd/rd cl)


The Circadian System


Photosensitive Retinal Ganglion Cells (pRGCs)

Blue Sensitive ~ 480nm

Melanopsin
Are humans like mice?

SC is an 88 year old patient with a genetic disease of the eye resulting in the loss of her rods and cones. No perception of light for 50 year
Normal Circadian Rhythms!

Despite no visual responses, individuals with no rods and cones can regulate their clocks by light!
Visual blindness need not result in loss of all light detection by the eye!

But.....sleep and 24h rhythm abnormalities are ignored in clinical ophthalmology
What is the impact of ocular disease on human sleep/wake biology?
Visual blindness need not mean complete blindness.

Such individuals have pRGCs and are being encouraged to expose their eyes to sufficient day-time light to maintain normal circadian entrainment and sleep-wake timing.
Diseases of the inner retina resulting in retinal ganglion cell death and optic nerve degeneration will inflict circadian rhythm and sleep disruption.

These individuals are now benefitting from treatments that consolidate sleep.
The clinical diagnosis of ‘complete’ blindness must assess the state of both the visual system and pRGCs.

Eye loss plunges individuals into a world that lacks both vision and a proper sense of time.

Clinical advice in ophthalmology must also incorporate the impact of eye diseases on sleep and circadian timing.

- 39 Million Blind
- 285 Million Visually Impaired
- 246 Million Low Vision
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lots of time of day effects ...... Athletic Performance
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### Graphs

**A**
- Plasma melatonin concentration (ng/mL)

**B**
- Core body temperature (°C)

**C**
- Subjective alertness (10 = very alert; 0 = very drowsy)

**D**
- Task performance reaction time (sec)

**E**
- Triglyceride concentration (mmol/L)

**Clock time (h)**

- 0600 - 1000
- 1200 - 1400
Athletic Performance

Circadian variation in swim performance

Christopher F. Kline, J. Larry Durstine, J. Mark Davis, Teresa A. Moore, Tina M. Devlin, Mark R. Zielinski, and Shawn D. Youngstedt

Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina

Submitted 17 August 2006; accepted in final form 1 November 2006

2.7 second difference over 200m

lots of time of day effects .......cognitive abilities
# Rhythmic Changes in Human Physiology and Behaviour

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![Graphs showing rhythmic changes](image)
Comparison of the effect of blood alcohol concentration (BAC) and time of day on task performance.

The dotted horizontal line is the mean performance at a blood alcohol concentration of 0.08% - the legal limit for driving in the UK.

Lamond and Dawson
J. Sleep Res. 1999 8: 255-262
Comparison of the effect of blood alcohol concentration (BAC) and time of day on task performance.

The dotted horizontal line is the mean performance at a blood alcohol concentration of 0.08% - the legal limit for driving in the UK.

Lamond and Dawson
J. Sleep Res. 1999 8: 255-262
.....lots of time of day effects ...... stroke
Circadian variation in incidence of stroke

Oxford Vascular Study (Peter M Rothwell)
.....lots of time of day effects ...... drug delivery
The right drug at the right amount at the right time for each individual!
Most drugs and treatments are not given on the basis of body time – but on the basis of **convenience** alone

But timing matters…..
Leukaemia
Disease-free survival rates were compared in 118 children who received chemotherapy (mercaptopurine and methotrexate)

Risk of relapse 2.56 x higher if chemotherapy given in the morning compared to evening.

.....lots of time of day effects ...... drug testing on rats and mice
Diurnal Mammal

Awake  |  Sleep

Delivery
Does 12h Matter?
Time of day effects: Susceptibility to trauma and toxins

Currently drug testing is performed on nocturnal rodents and extrapolated to a diurnal species such as ourselves.

Responses may be very different at different times of the day!

Fig. 7.10  Susceptibility rhythm of mice to intraperitoneal injections of E. coli endotoxin. A dose compatible with survival for most animals at one time of day is highly lethal when injected into comparable mice at a different circadian phase. (After Halberg, 1960.)

Exposure to bacterial toxin
Introduction – The Body Clock

Light Regulation of The Body Clock

Time of Day Effects

Disruption of the Body Clock

Discussion
Society is sleep deprived!
Self-reported weekday sleep (hours)

University of Chicago
2001
Survey Study
Dr. Eve Van Cauter

18-25  35-50  60-75
Age (years)
Mary Carskadon at Brown University has shown that, on average, US teenagers are getting about 7.5 hours a night's sleep on school nights, but as many as 25% get fewer than 6.5 hours per night. Carskadon estimates that to be optimally alert, teenagers need approximately 9 hours of sleep.
It is even worse for shift-workers....
Night Shift

> 20% of the economy in the developed and developing nations
Most night shift-workers do not shift their physiology in response to the demands of working at night.
WHY?
### Rhythmic Changes in Human Physiology and Behaviour

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melatonin</strong></td>
<td>Low</td>
<td>High</td>
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<tr>
<td><strong>Cortisol</strong></td>
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<td>Low</td>
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<tr>
<td><strong>Body Temperature</strong></td>
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<td>Low</td>
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<tr>
<td><strong>Catecholamines</strong></td>
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<td>Low</td>
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<tr>
<td><strong>Urine Production</strong></td>
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<td>Low</td>
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<tr>
<td><strong>Growth Hormone</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Alertness and Cognitive Performance</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Lapses in Attention</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Memory Recall</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Capacity to Digest Fat</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Muscular Strength</strong></td>
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![Graphs showing changes in physiological and behavioral markers over the day and night.](image)
Many night shift-workers get 5.5h or less sleep every 24hs.
Consequences of Disrupted Sleep

- Drowsiness/Microsleeps/Unintended Sleep
- Abrupt mood shifts
- Increased irritability
- Anxiety and depression
- Weight gain
- Decreased socialization skills & sense of humor
- Decreased motor performance
- Decreased cognitive performance
- Reduced ability to concentrate & remember
- Reduced communication & decision skills
- Increased risk-taking
- Reduced quality, creativity & productivity
- Reduced immunity to disease and viral infection.
- Feelings of being chilled
- Reduced ability to handle complex tasks or multi-task
Night-shift workers in a nuclear power plant.

- 60% of workers fall asleep 1/week
- 25% of workers fall asleep 4-5/week
- 15% of workers fall asleep 10/week

- 33% of workers admitted that falling asleep had caused a significant error or near-miss once/year

- All 5 controllers were found asleep – and did not appreciate that they had fallen asleep
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Sleep Gain

Hormone - Leptin

Decreased Hunger

Weight Loss

Sleep

Hormone - Ghrelin

Increased Hunger

Weight Gain
<table>
<thead>
<tr>
<th>Hours of sleep per night</th>
<th>% likelihood of being obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4h</td>
<td>73%</td>
</tr>
<tr>
<td>~5h</td>
<td>50%</td>
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<tr>
<td>~6h</td>
<td>23%</td>
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Effect of sleep deprivation on brain activation while performing mathematical tasks (fMRI)
Effect of sleep deprivation on brain activation while performing mathematical tasks (fMRI)
Consequences of Disrupted Sleep

- Drowsiness/Microsleeps/Unintended Sleep
- Abrupt mood Shifts
- Increased irritability
- Anxiety and depression
- Metabolic Problems - Weight gain/loss
- Decreased socialization skills & sense of humor
- Decreased motor performance
- Decreased cognitive performance
- Reduced ability to concentrate & remember
- Reduced communication & decision skills
- Increased stimulant and sedative use
- Increased risk-taking
- Reduced creativity & productivity
- Reduced immunity to disease and viral infection.
- Feelings of being chilled
- Reduced ability to multi-task
Stimulant/Sedation feed-back loop
Stimulant/Sedation feed-back loop
• Introduction – The Body Clock
• Light Regulation of The Body Clock
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• Disruption of the Body Clock
• Discussion
Sleep Hygiene!
Do

Go to bed at the same time each day.
Get up from bed at the same time each day.
Get regular exercise each day, preferably in the morning.
Get regular exposure to outdoor or bright lights.
Keep the temperature in the bedroom cool.
Keep the bedroom quiet when sleeping.
Keep the bedroom dark enough to facilitate sleep.
Keep feet and hands warm.

Don’t

Watch television in bed.
Work at a computer just before bed.
Argue just before bed.
Have caffeine in the evening.
Use alcohol to help you sleep.
Go to bed too hungry or too full.
Take another person’s sleeping pills.
Take over-the-counter sleeping pills.
Take naps over 20-30 min.
Command yourself to go to sleep.