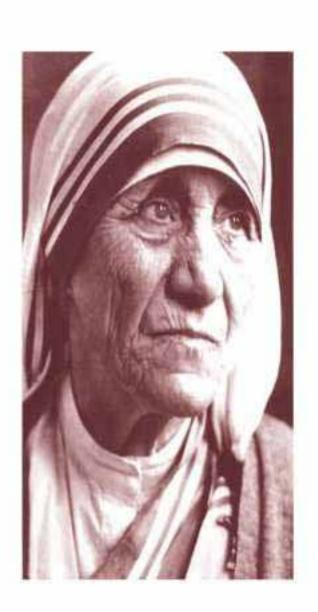
#### ....and finally

Does time really pass faster as we get older?

Come to the next lecture on 25th March 2004

Turning back the hands of time: growing old gracefully



# Biological clocks: human and animal concepts of time



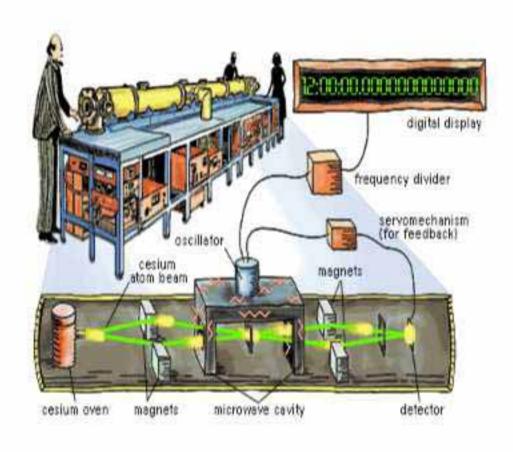


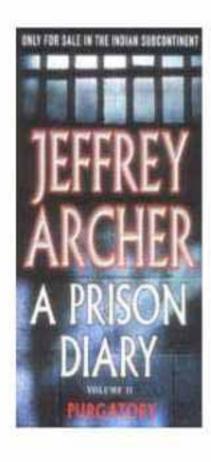
#### The fourth dimension

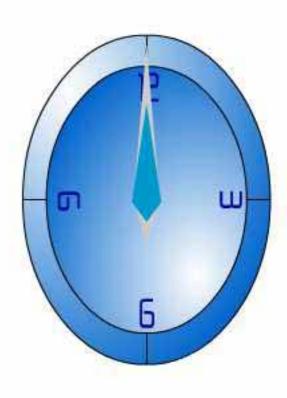
We surround ourselves with keepers of the fourth dimension:

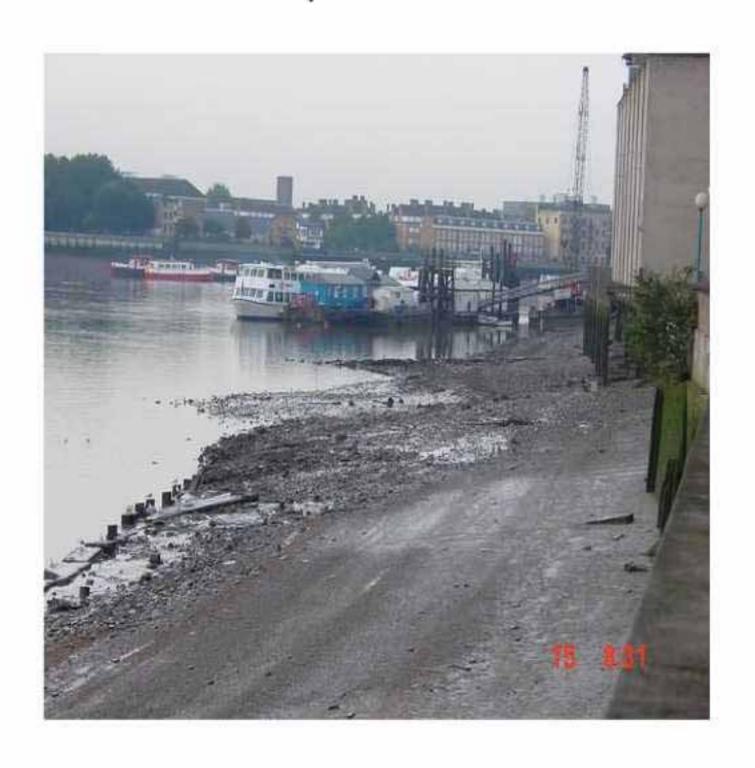
### The fourth dimension

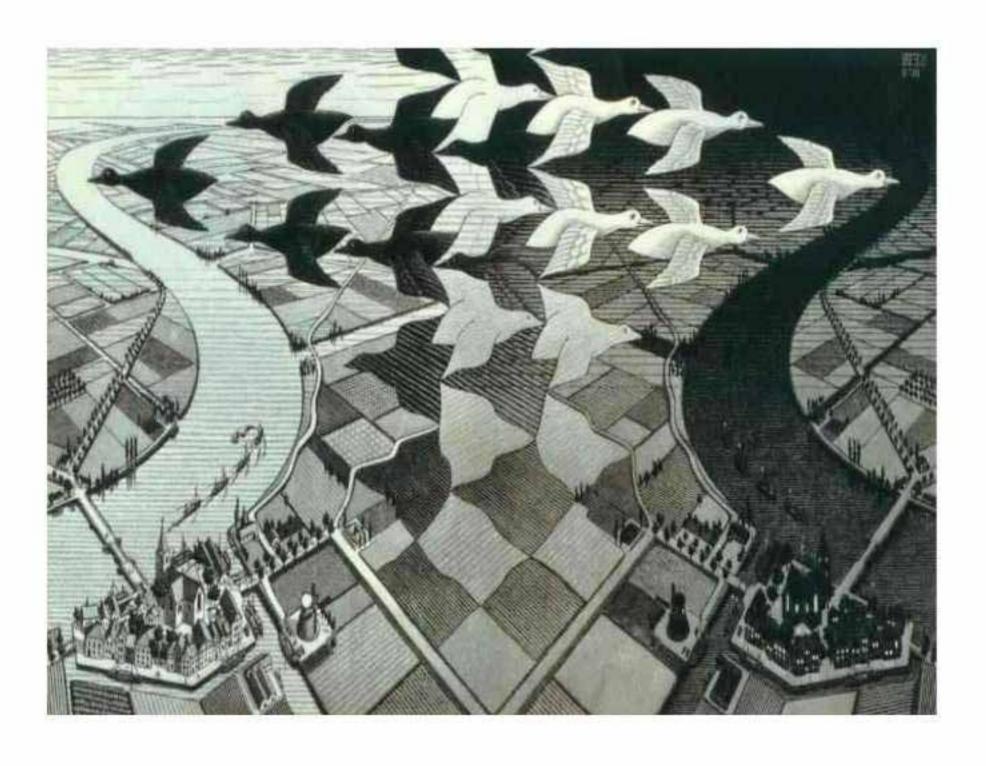
We surround ourselves with keepers of the fourth dimension: TIME



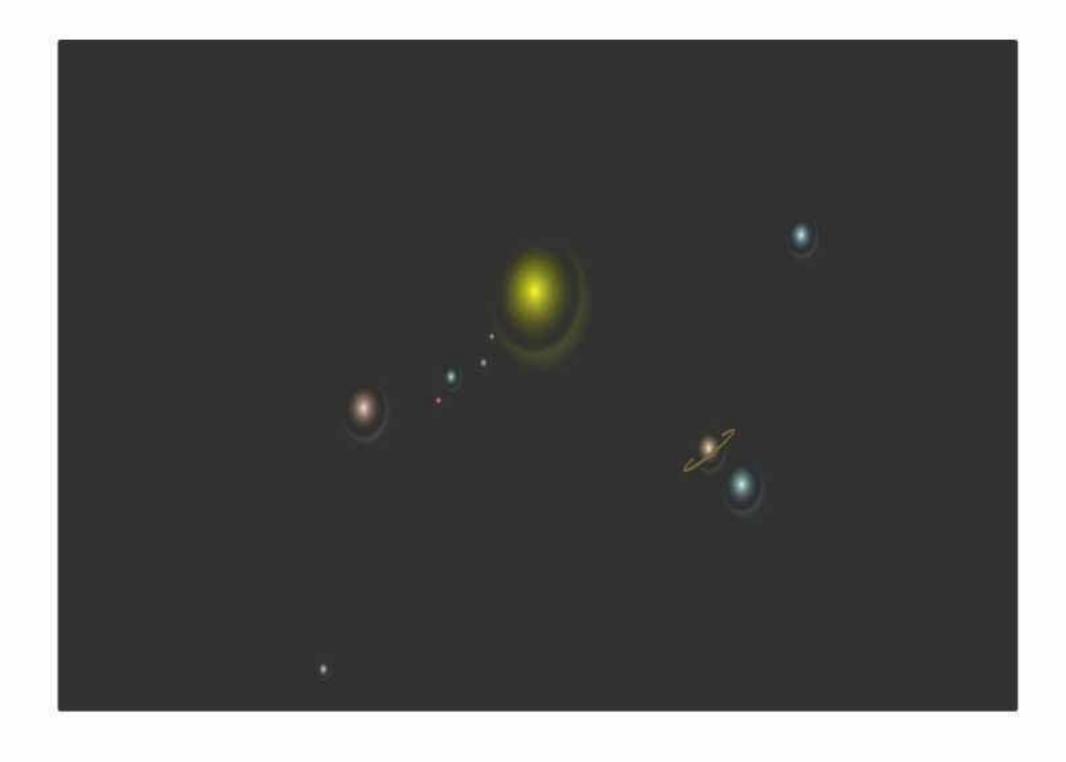












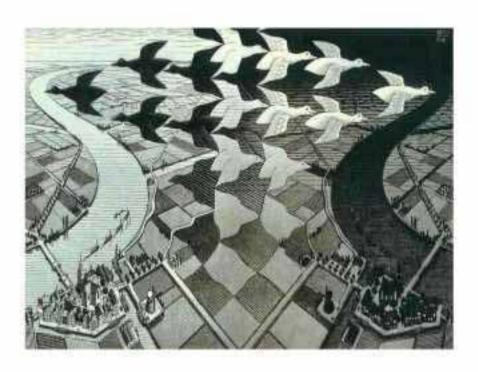
Question: With all these external zeitgebers (time-givers)

is there any need for biological clocks?

Answer: Yes



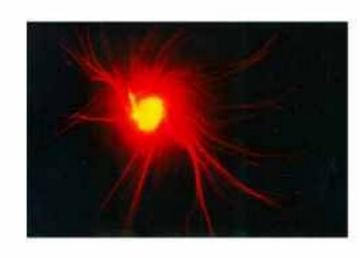


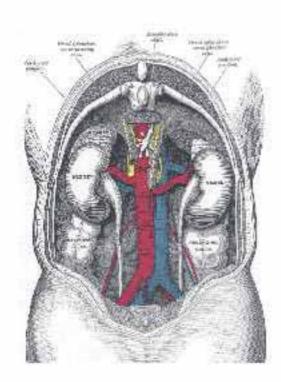


Question: With all these external zeitgebers (time-givers) is there any need for biological clocks?

Answer: Yes, all biological organisms from single cells to whole organs from plants to animals, including

humans, have them





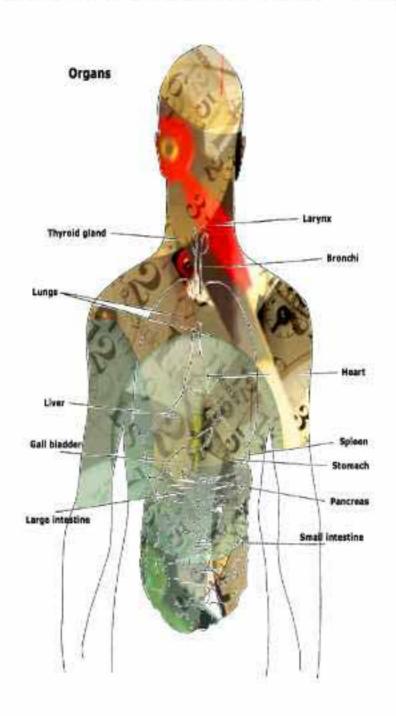




Our bodies resemble the classic nightmare shop full of ticking and chiming clocks which are only stopped by death



Our bodies resemble the classic nightmare shop full of ticking and chiming clocks which are only stopped by death



Biological clocks are fuelled by the energy we derive from food



Biological clocks are fuelled by the energy we derive from food

They rely on external zeitgebers to keep them in phase with nature



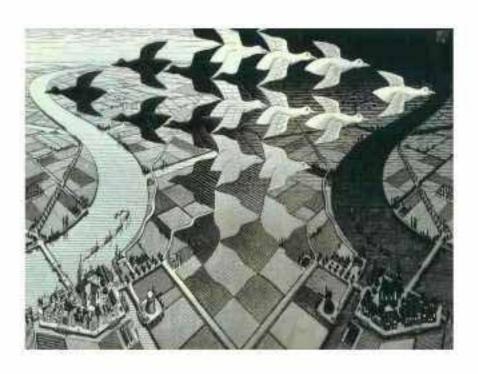




We don't just dance to the rhythms of the world around us

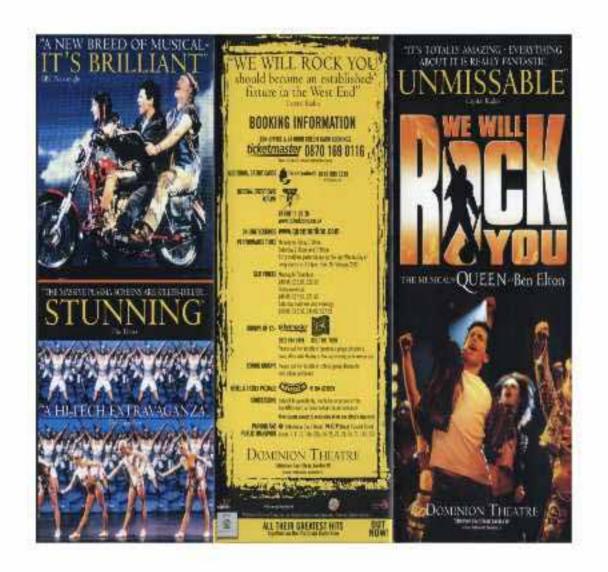






We don't just dance to the rhythms of the world around us

We dance to our own tunes but in harmony with the rhythms going on around us



We don't just dance to the rhythms of the world around us

We dance to our own tunes but in harmony with the rhythms going on around us

The bad news is time flies -

We don't just dance to the rhythms of the world around us

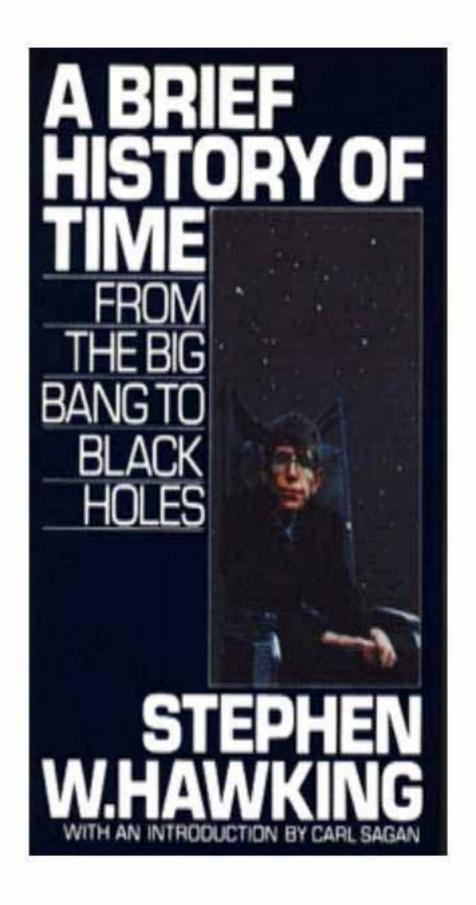
We dance to our own tunes but in harmony with the rhythms going on around us

The bad news is time flies The good news is you're the pilot
(Michael Althsuler)



### Why do we need to know about them?

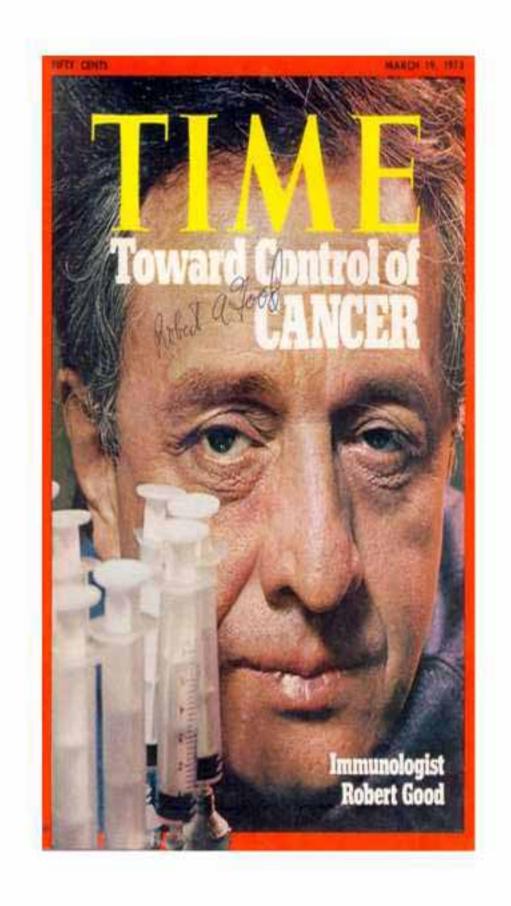
Understanding dimensional and cosmological time may reveal how to travel in time and the origins of the universe



# Why do we need to know about them?

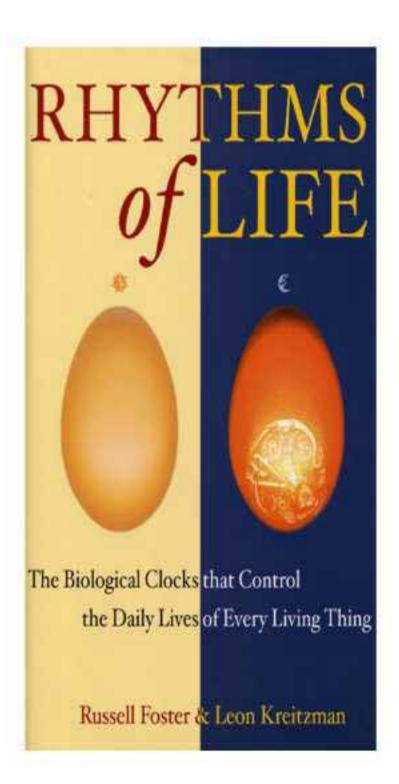
Understanding dimensional and cosmological time may reveal how to travel in time and the origins of the universe

Understanding biological time will reveal not only how our bodies function but also how to treat or prevent major human diseases



Rhythms of Life

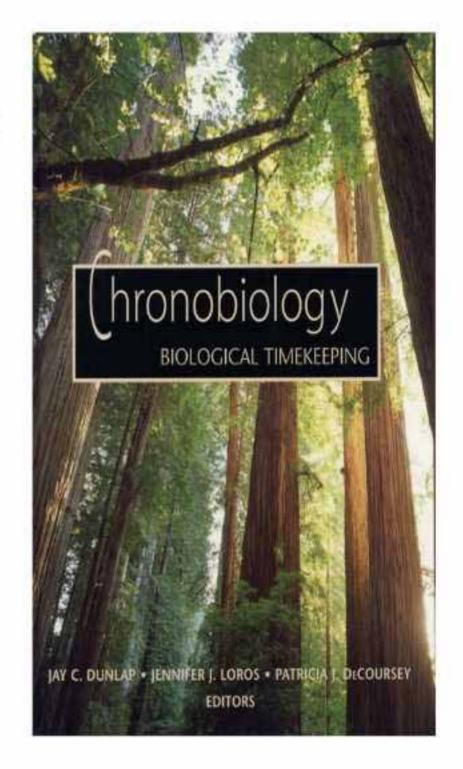
Foster and Kreitzman (2004)



Rhythms of Life

Foster and Kreitzman (2004)

Chronobiology: Biological Timekeeping Dunlap et al (2004)



Rhythms of Life

Foster and Kreitzman (2004)

Chronobiology: Biological Timekeeping

Dunlap et al (2004)

Mimosa plants de Mairan (1729)



Rhythms of Life Foster and Kreitzman (2004)

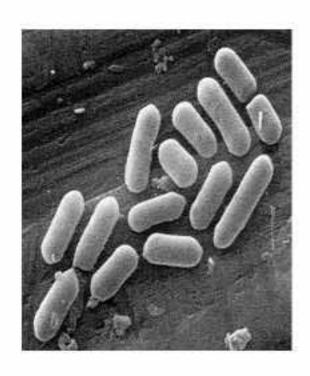
Chronobiology: Biological Timekeeping Dunlap et al (2004)

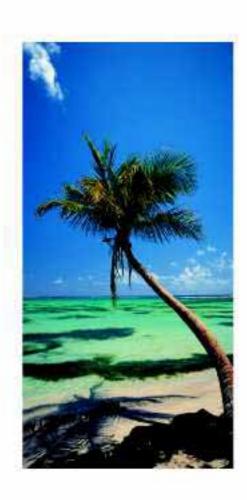
Mimosa plants de Mairan (1729)

The common bean plant Erwin Bünning (1930)



Numerous internally regulated biological rhythms have now been established in both plant and animal kingdoms







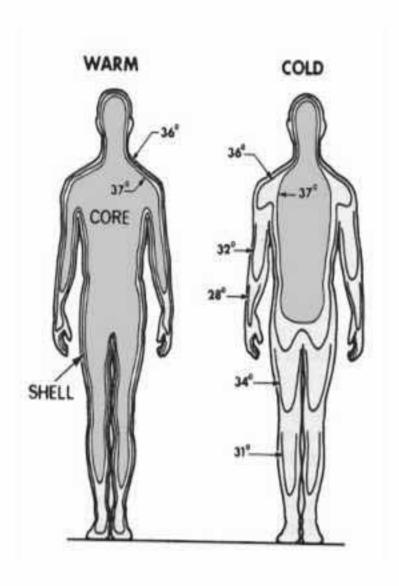
Biological clocks are quite accurate (usually about ±0.5%)



Linné (1751)

Biological clocks are quite accurate (usually about  $\pm 0.5\%$ )

They have in-built temperature compensation



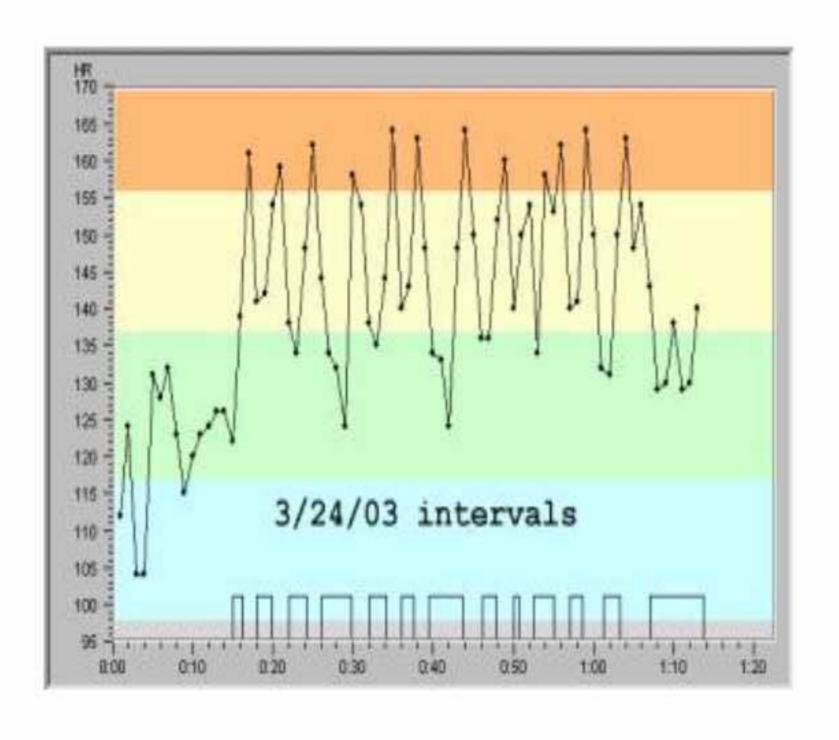
Biological clocks are quite accurate (usually about  $\pm 0.5\%$ )

They have in-built temperature compensation

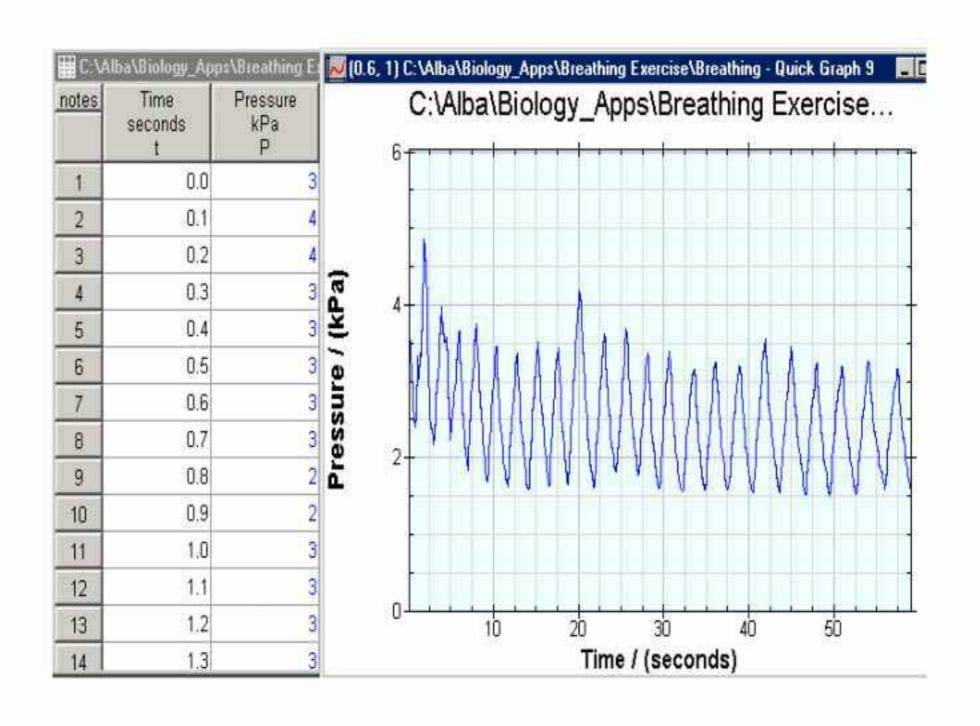
In many cases these can be entrained in response to external light cues

Some can also be entrained in response to food

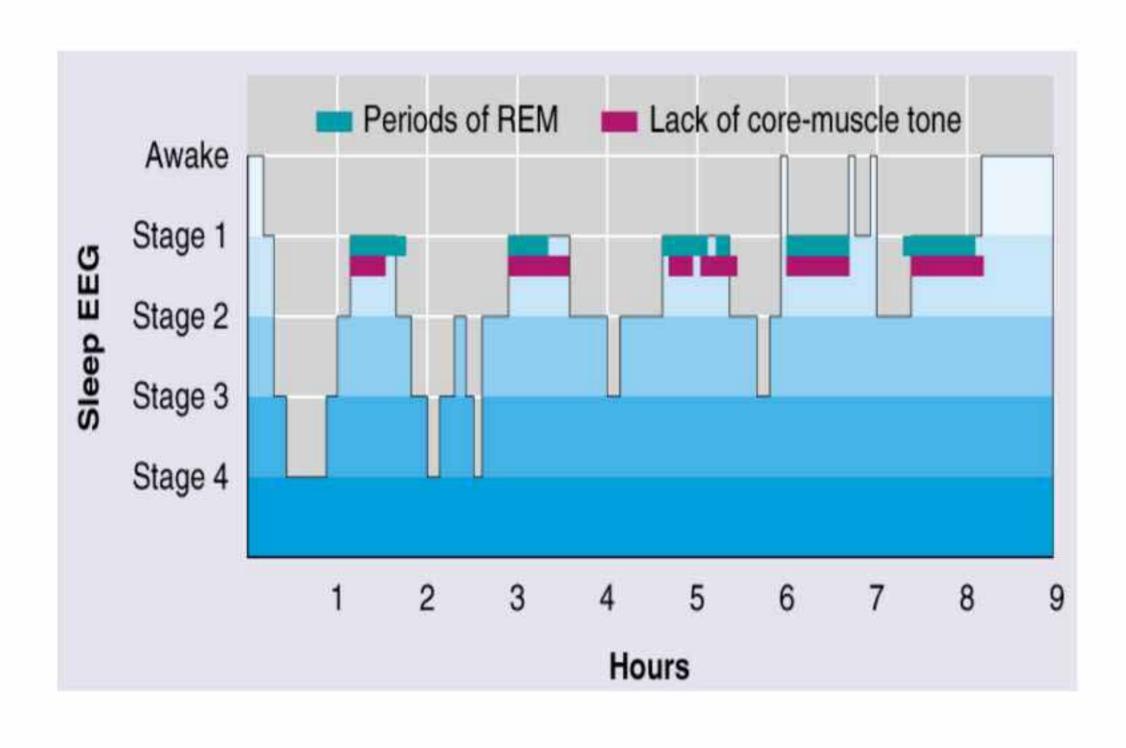
All organisms have ultradian cycles (<24h)



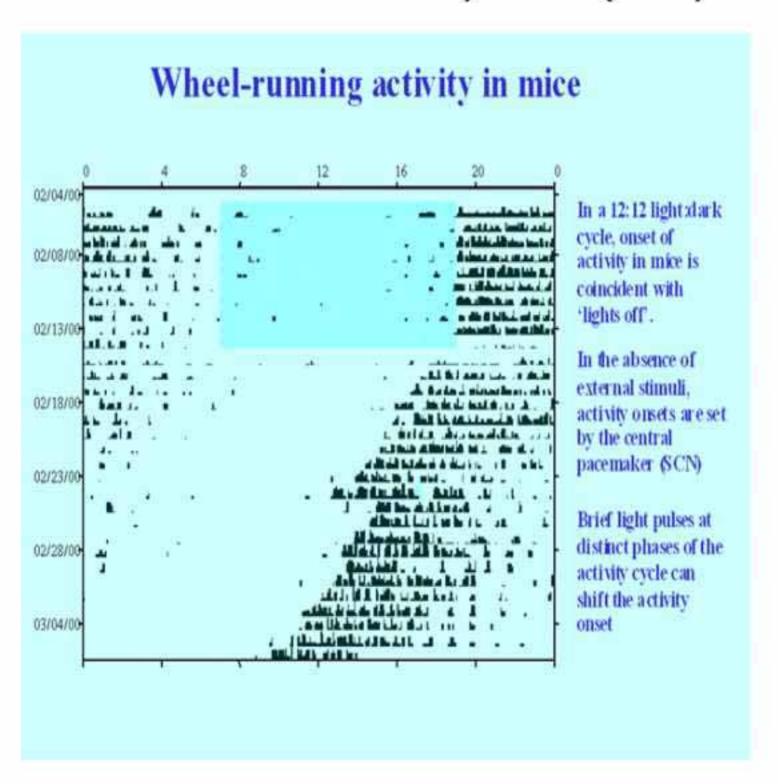
# All organisms have ultradian cycles (<24h)



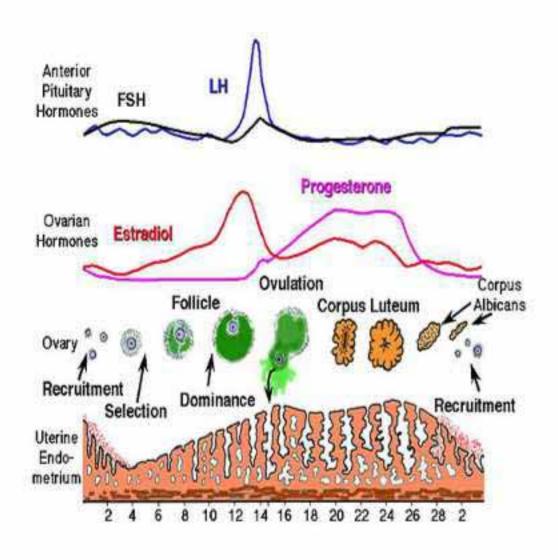
All organisms have ultradian cycles (<24h)



All organisms exhibit circadian rhythms (24h)



# Many have infradian cycles (>24h)

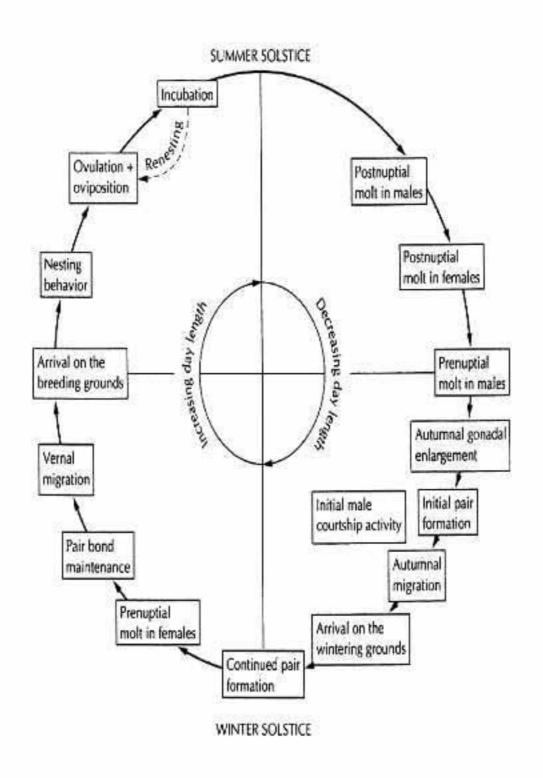


Human menstrual cycle



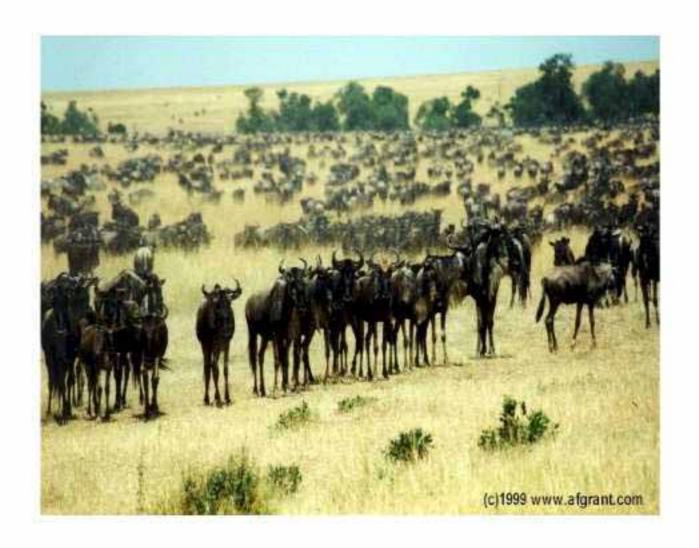
Atlantic fireworm fertilisation on the night before each quarter moon

# Some show circannual cycles (>1 year)



Some show circannual cycles (>1 year)

- seasonal breeding, migration and hibernation



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Bamboo plants flower every 7 years





### Examples of innate rhythms

Some show circannual cycles (>1 year)

- seasonal breeding, migration and hibernation

Bamboo plants flower every 7 years

Cicada reproductive peak two weeks every 13 or 17 years



### Examples of innate rhythms

Some show circannual cycles (>1 year)

- seasonal breeding, migration and hibernation

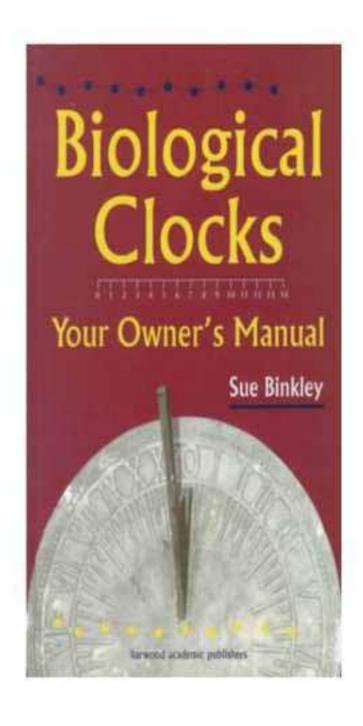
Bamboo plants flower every 7 years

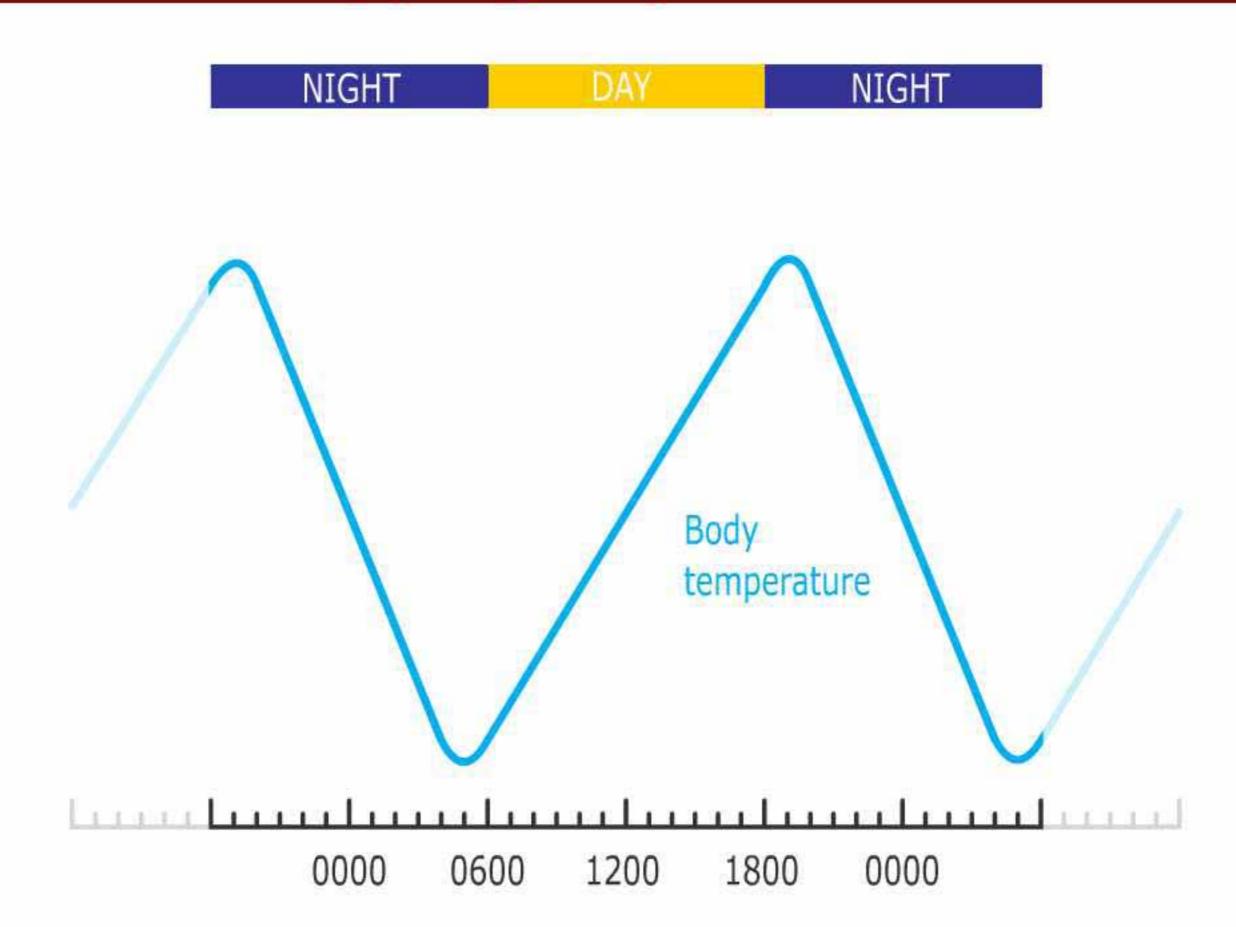
Cicada reproductive peak two weeks every 13 or 17 years

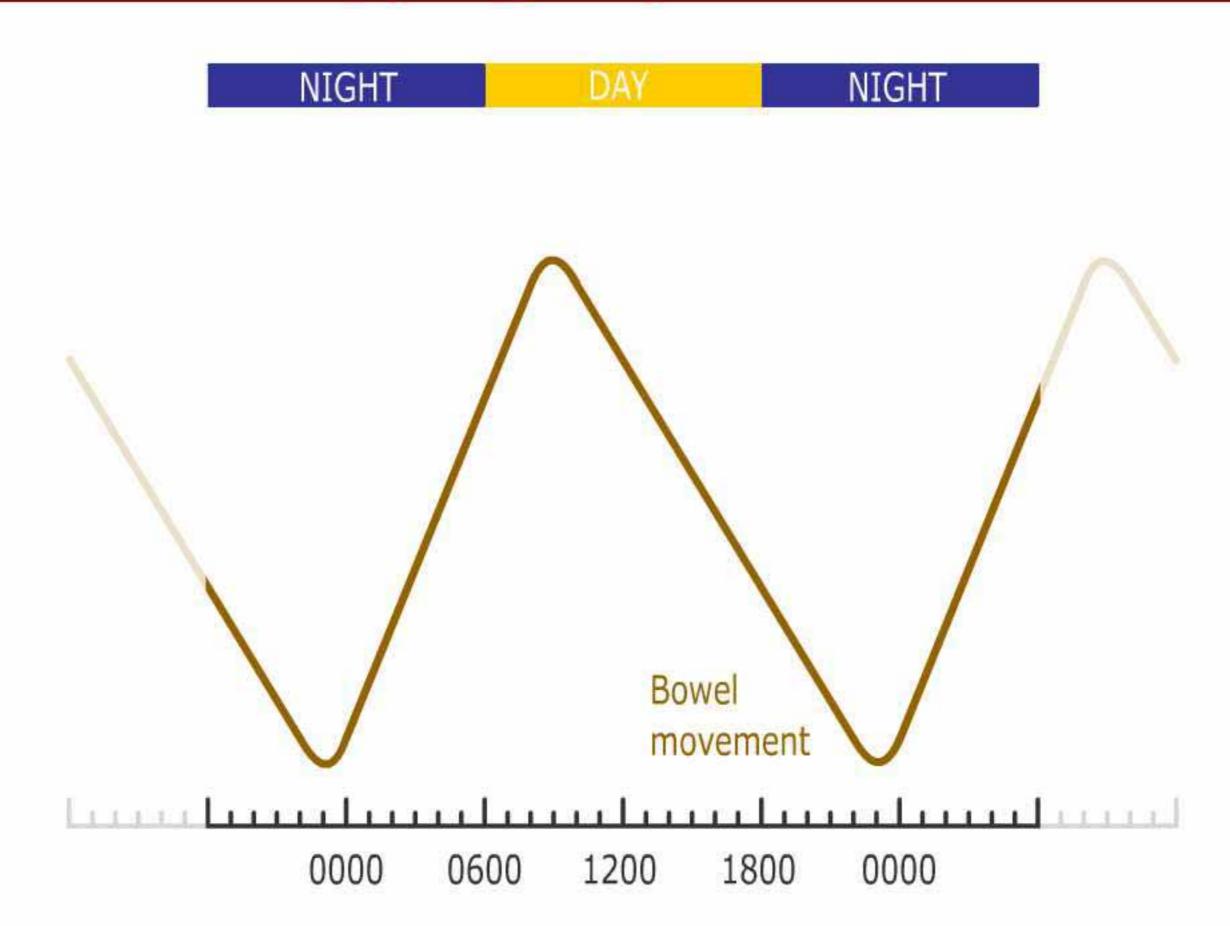
Agave Americana only flowers once every 100 years

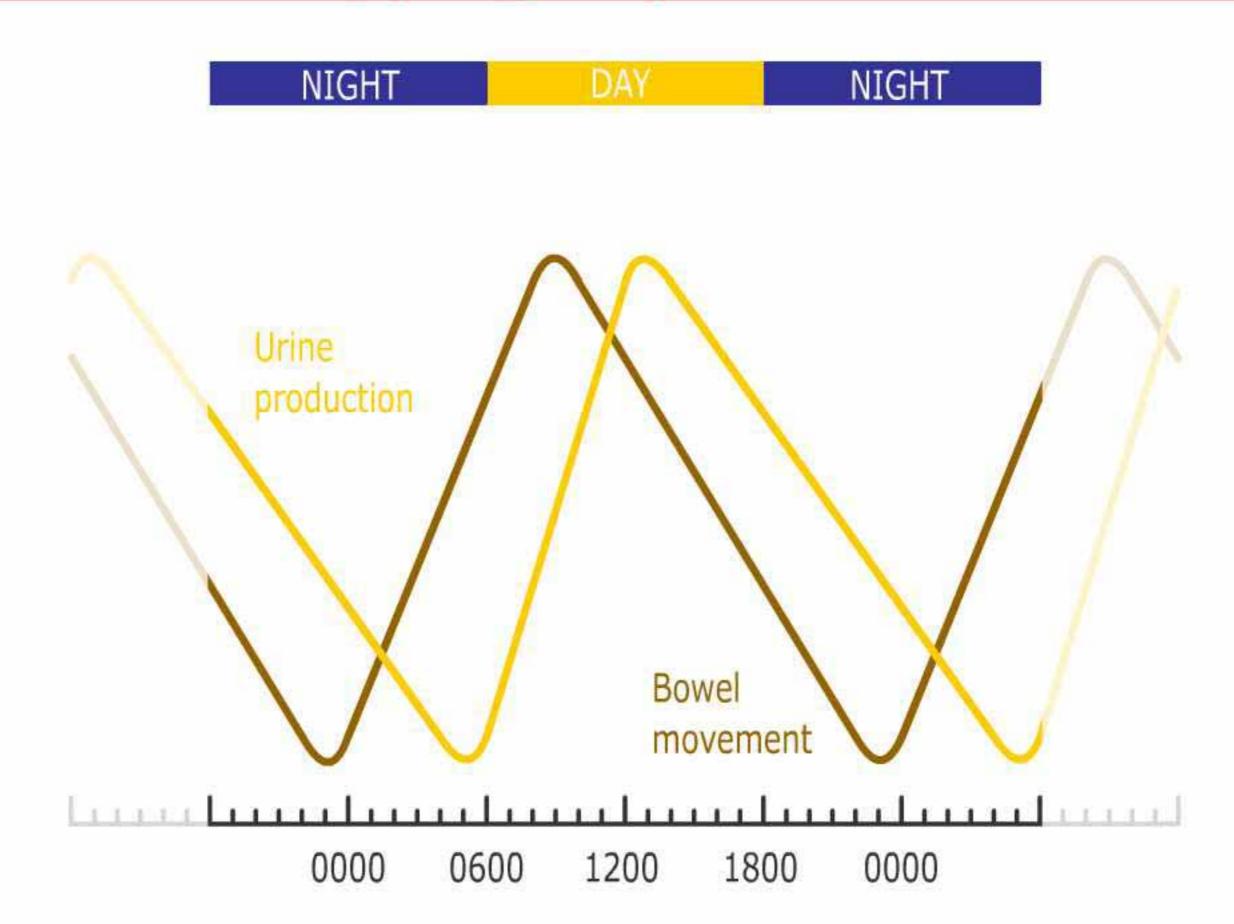


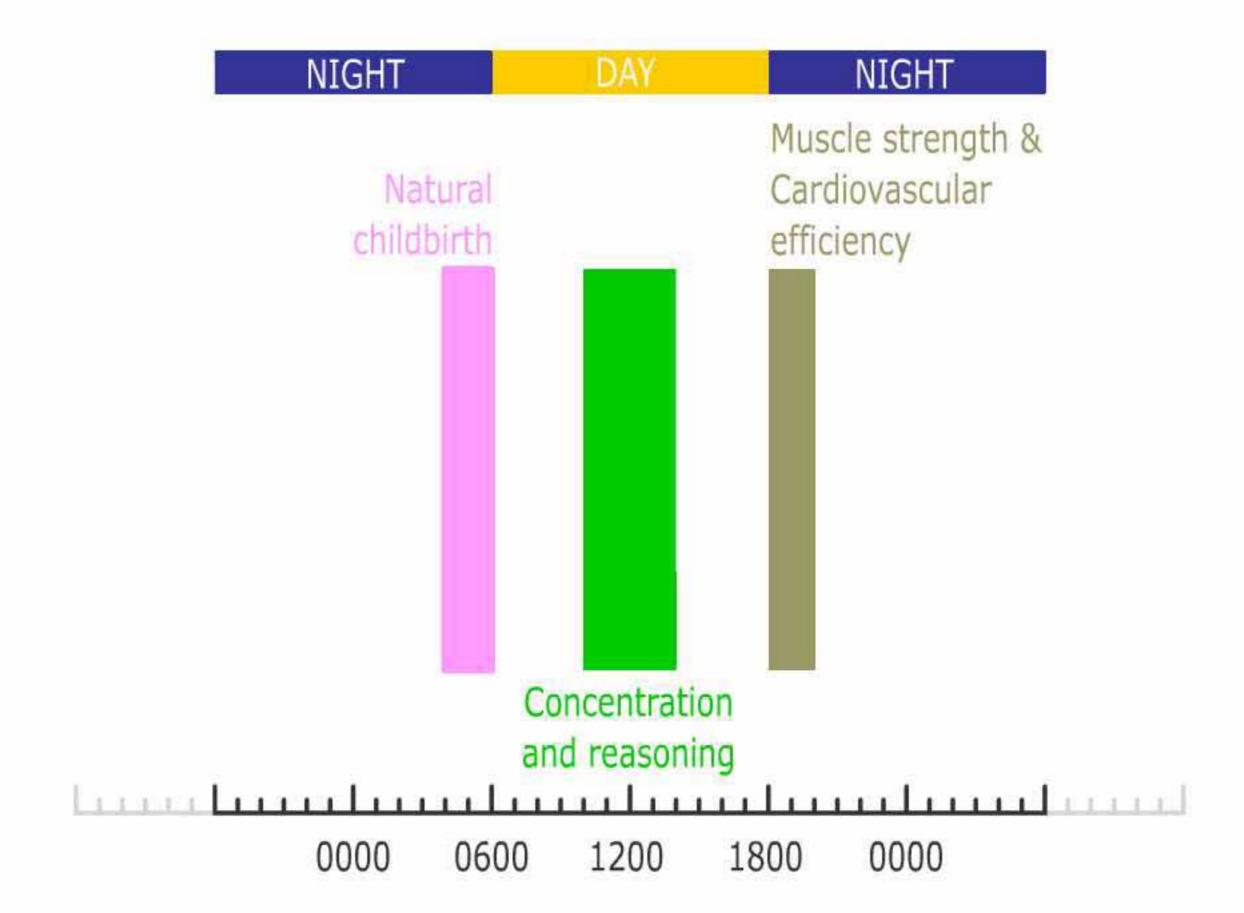
There is indeed a biological time for everything!



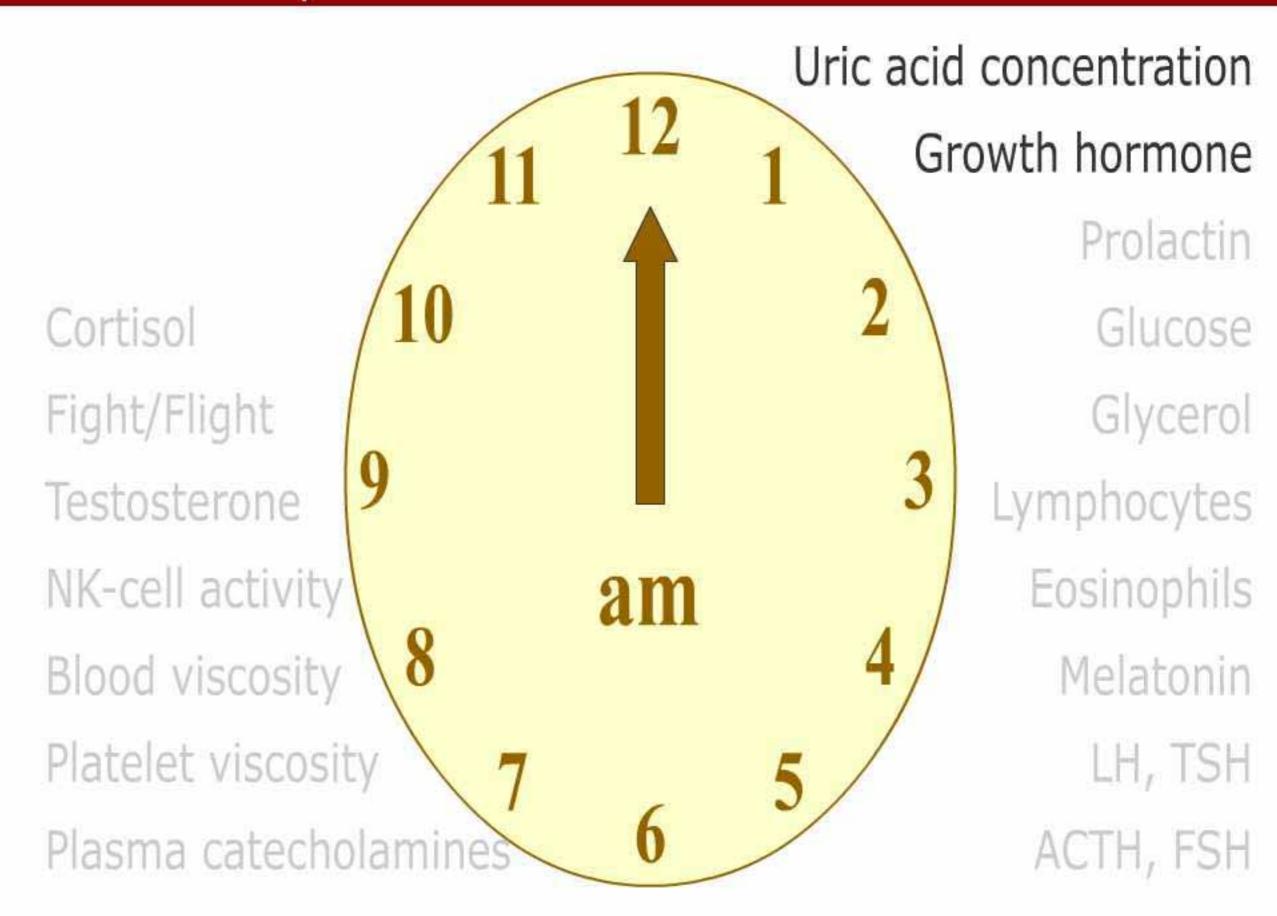




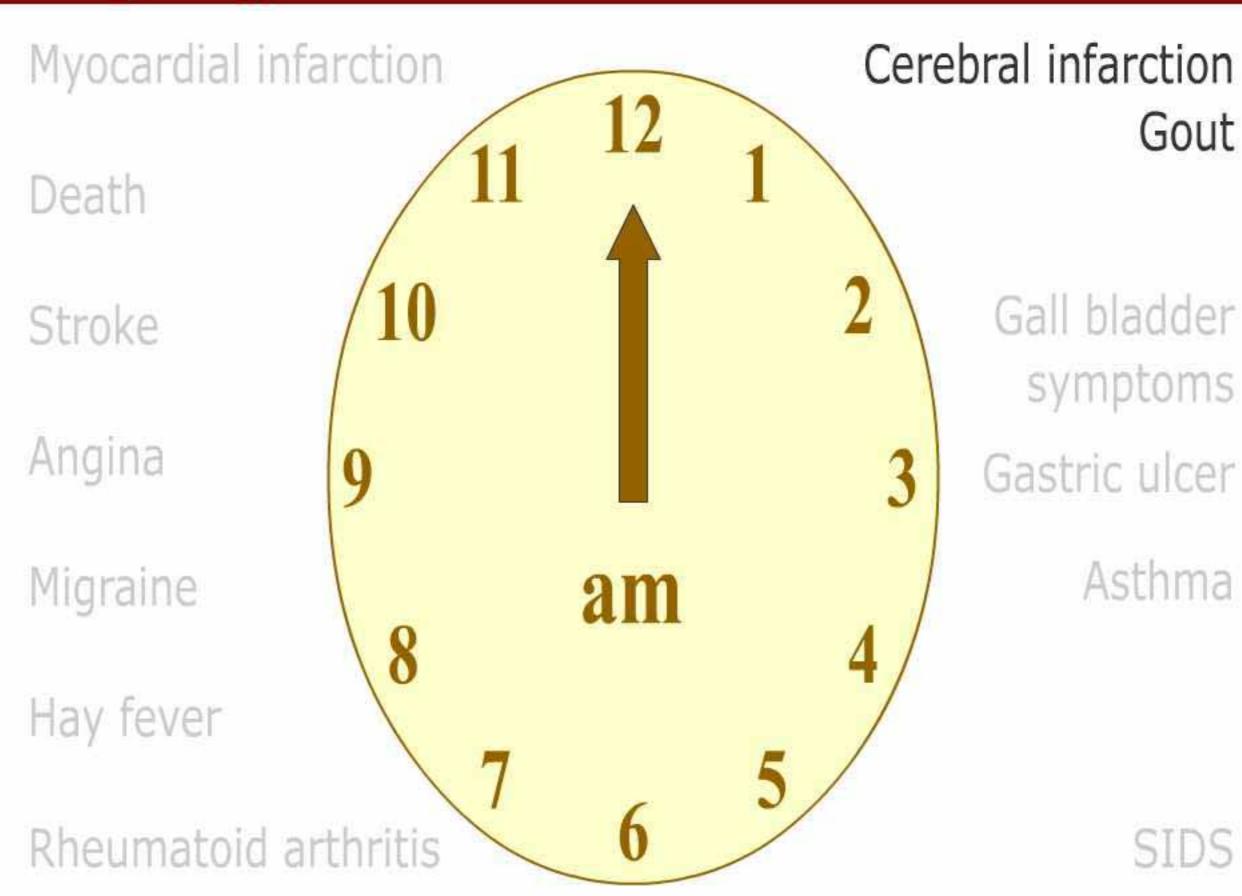




### Biochemical cycles



### Susceptibility to disease

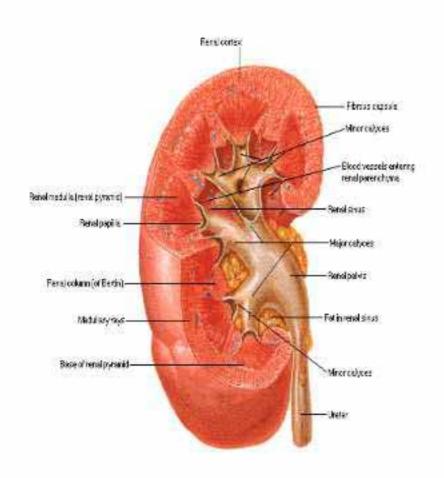


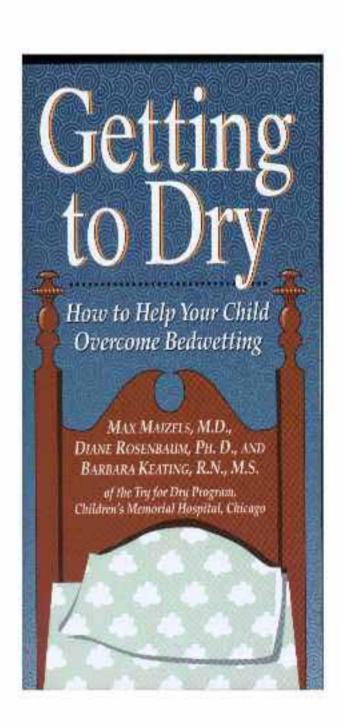
Time is God's way of keeping everything from happening at once



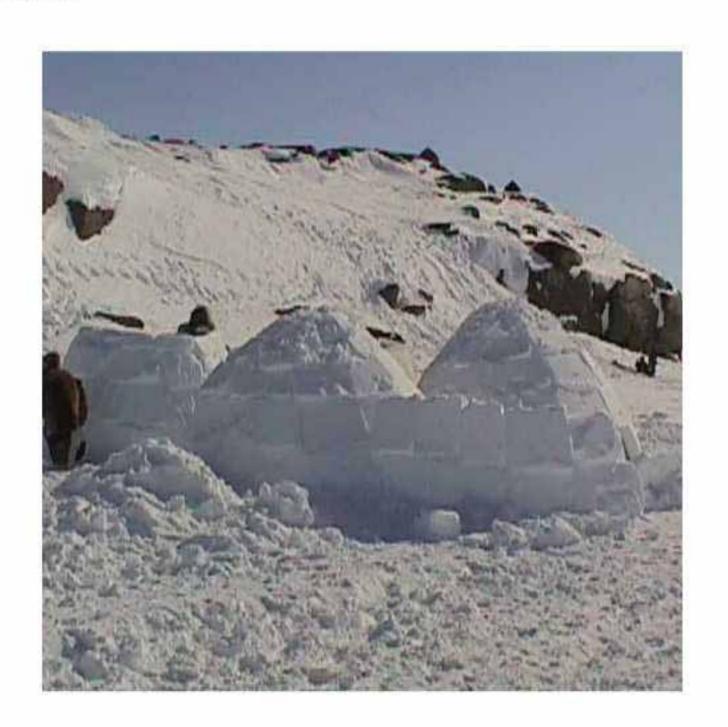
Time is God's way of keeping everything from happening at once

Your kidneys take a rest at night so you don't have to wake up for a pee!





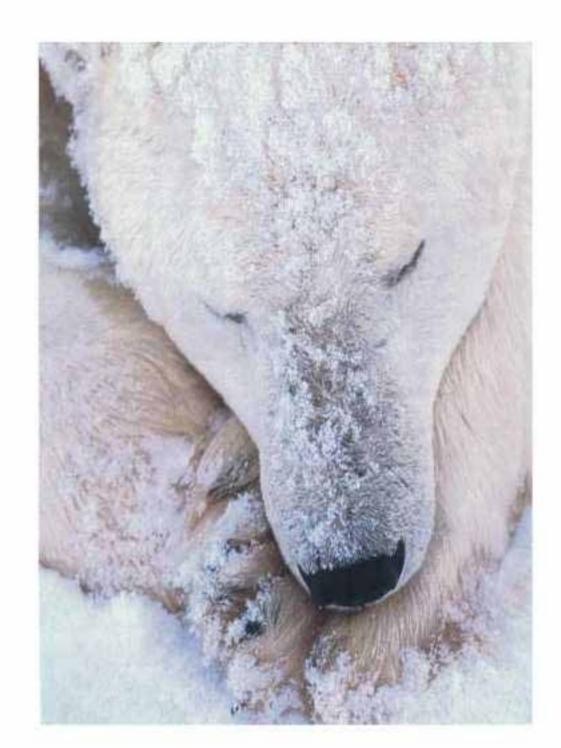
There's no point producing kids when it's -30°C outside and there's no food



There's no point producing kids when it's -30°C outside and

there's no food

Migrating or hibernating at the wrong time would be a problem

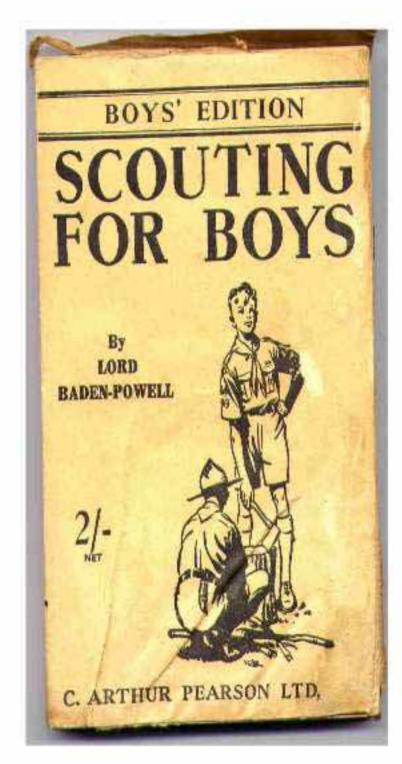


There's no point producing kids when it's -30°C outside and

there's no food

Migrating or hibernating at the wrong time would be a problem

Being prepared



There's no point producing kids when it's -30°C outside and there's no food

Migrating or hibernating at the wrong time would be a problem

Being prepared

Getting out of the noon day sun

Waking up ready for action



There's no point producing kids when it's -30°C outside and

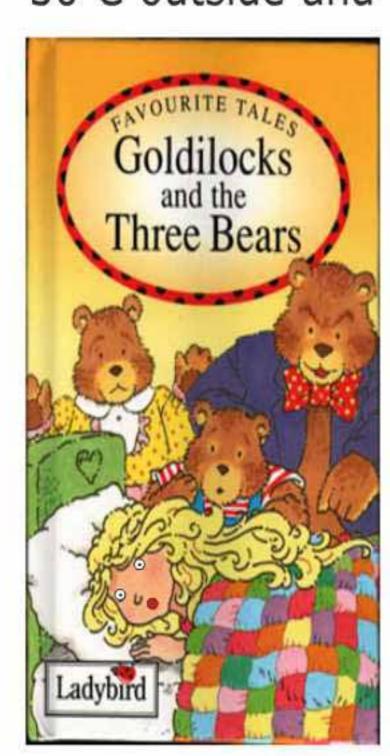
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Being prepared

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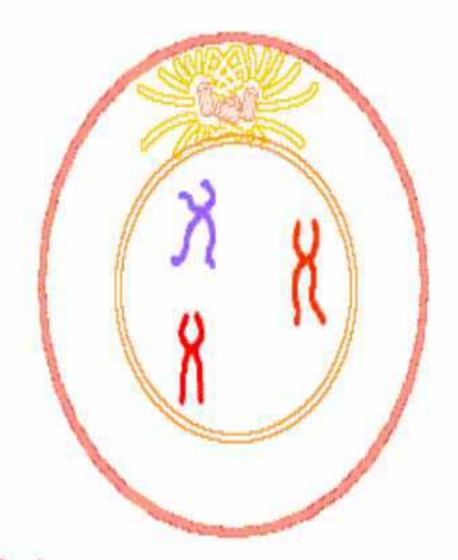
Waking up ready for action



A biological clock allows us to anticipate nature as well as exist in harmony with it



## Cellular clocks: all cells can show cyclic activity

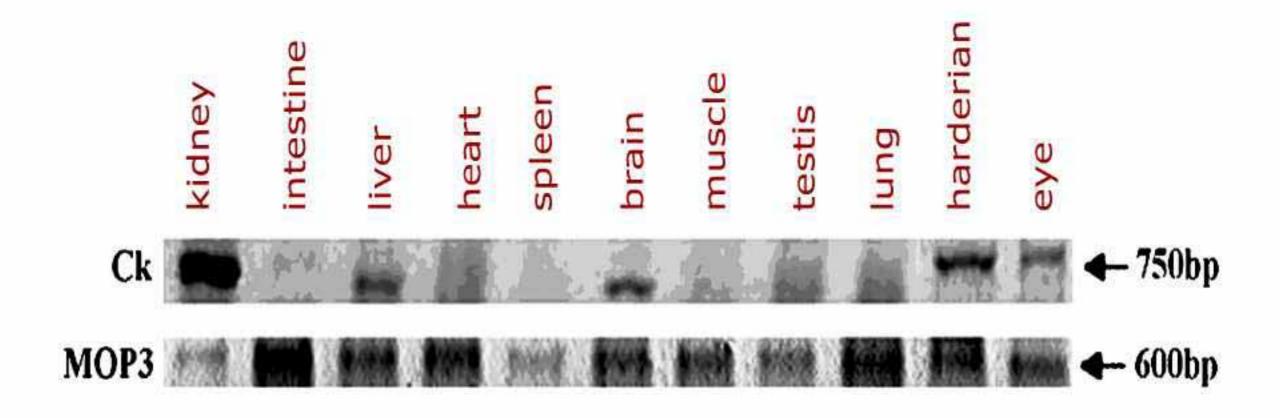


#### Prophase:

- · condensation of chromosomes
- · disappearance of nucleoli and nuclear envelope

Cellular clocks: all cells can show cyclic activity

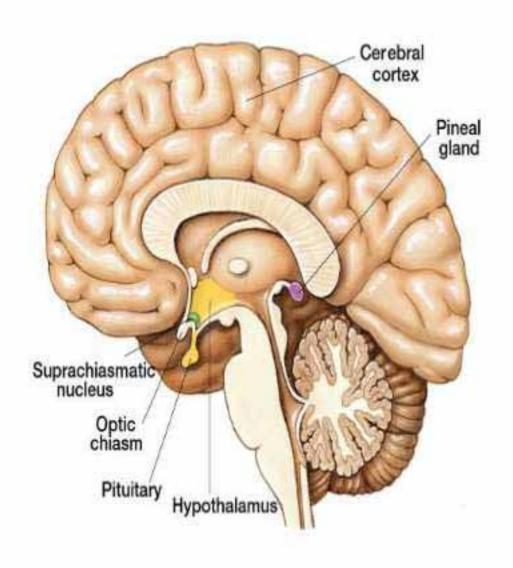
Body clocks: heart, liver, kidneys and embryos



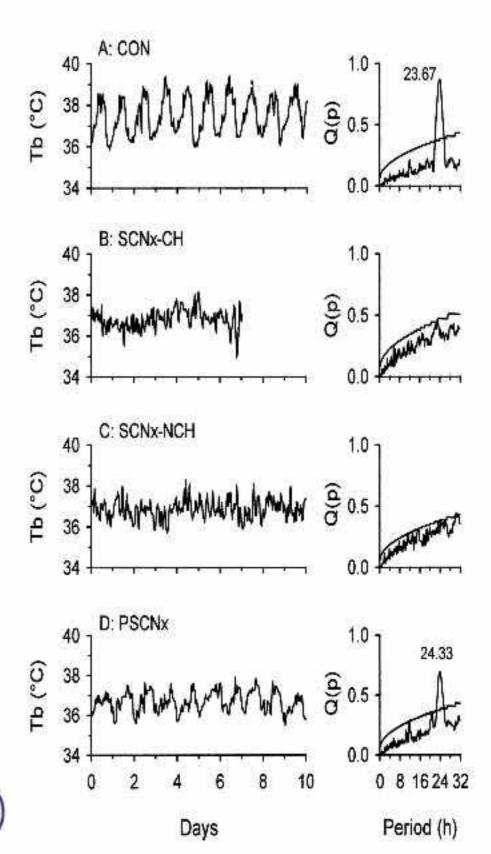
Tissue distribution of Clock and MOP3 in the mole rat. Avivi et al PNAS 2001

Brain clocks: the suprachiasmatic nucleus (SCN)

20,000 neurones under the neocortex



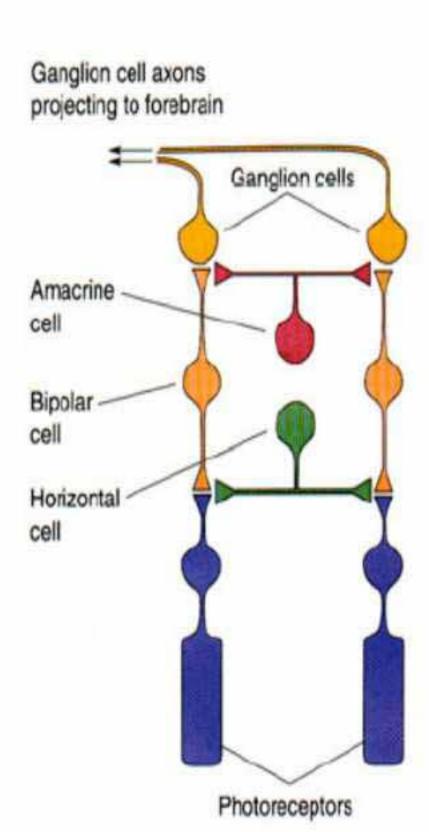
With no SCN normally rhythmic cycles become arrhythmic



Ruby et al J. Neuroscience (2002)

With no SCN normally rhythmic cycles become arrhythmic

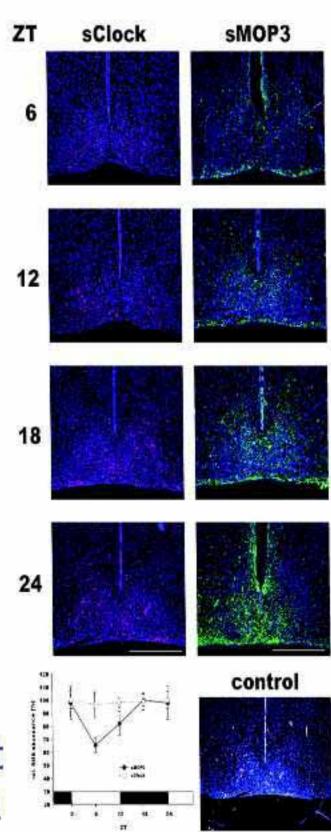
SCN receives direct projections from special photoreceptors



With no SCN normally rhythmic cycles become arrhythmic

SCN receives direct projections from special photoreceptors

The blind can still sometimes show photoperiodic responses

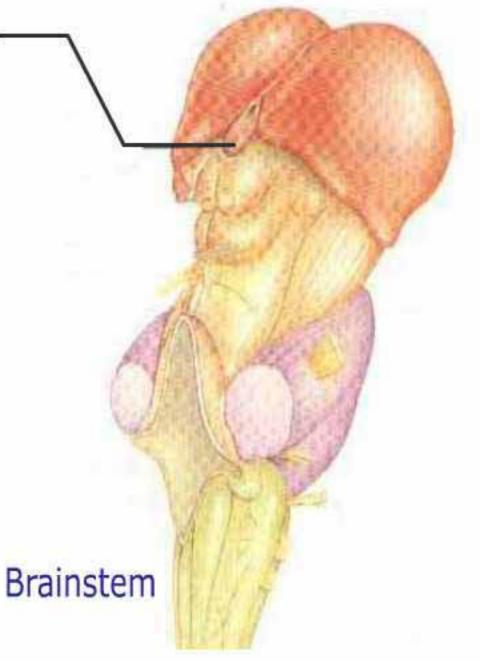


Oscillation of MOP3 in the blind mole rat Avivi et al PNAS 2001

How does the SCN clock communicate time to the brain?

Direct connections to the pineal gland -

Regulates release of melatonin

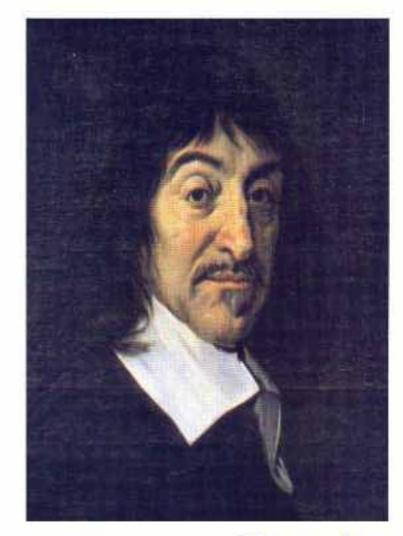


How does the SCN clock communicate time to the brain?

Direct connections to the pineal gland

Regulates release of melatonin

Pineal gland is not the seat of the soul



Descartes

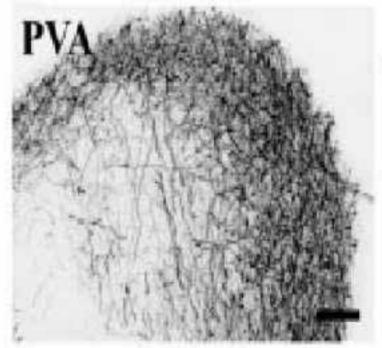
How does the SCN clock communicate time to the brain?

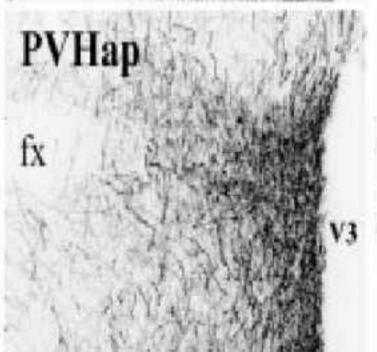
Direct connections to the pineal gland

Regulates release of melatonin

Pineal gland is not the seat of the soul

SCN connections with the rest of the brain are sparse





Kriegsfeld et al J. Comp. Neurology (2004)

Fetal SCN grafts restore rhythmic function in animals with no SCN

48 hours **LESION ARRHYTHMIA GRAFT** RHYTHM RESTORED Lehman et al J. Neuroscience 1987

Fetal SCN grafts restore rhythmic function in animals with no SCN

The Syrian Hamster tau mutation - a 22 vs 24.1h clock

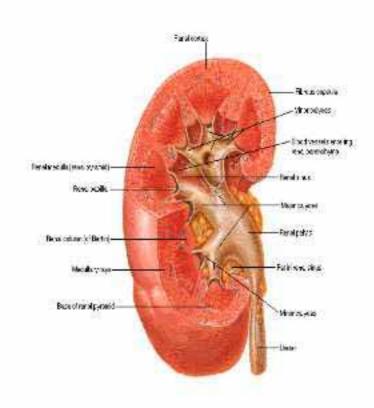
SCN must be able to communicate time chemically



The only chemical messengers identified so far are:

Arginine vasopressin



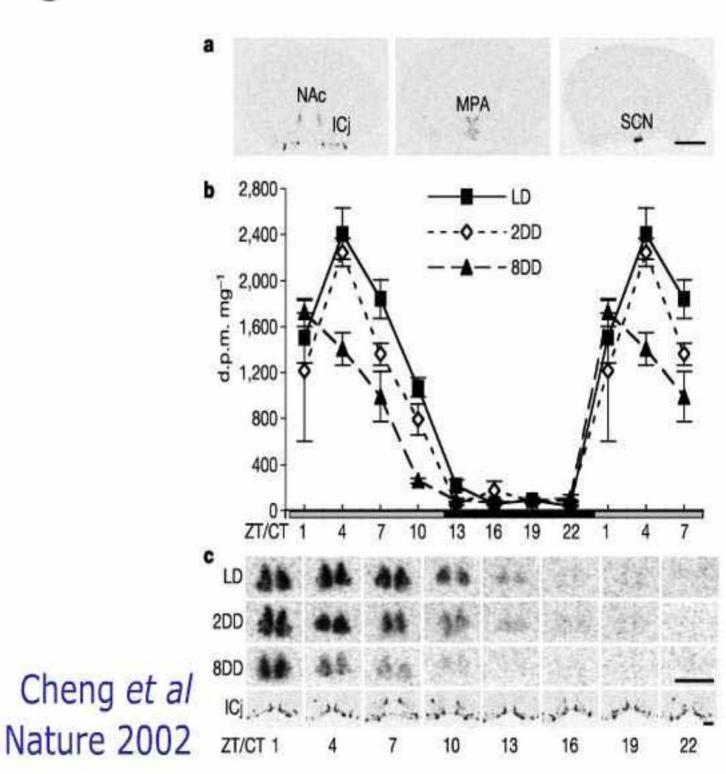




The only chemical messengers identified so far are:

Arginine vasopressin

Prokineticin



The brain clock and seasonal rhythms

Seasonal reproductive, migratory and hibernation behaviours







The brain clock and seasonal rhythms

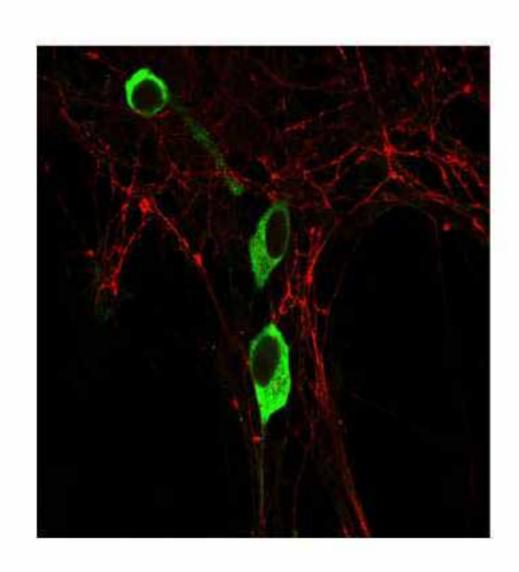
Seasonal reproductive, migratory and hibernation behaviours

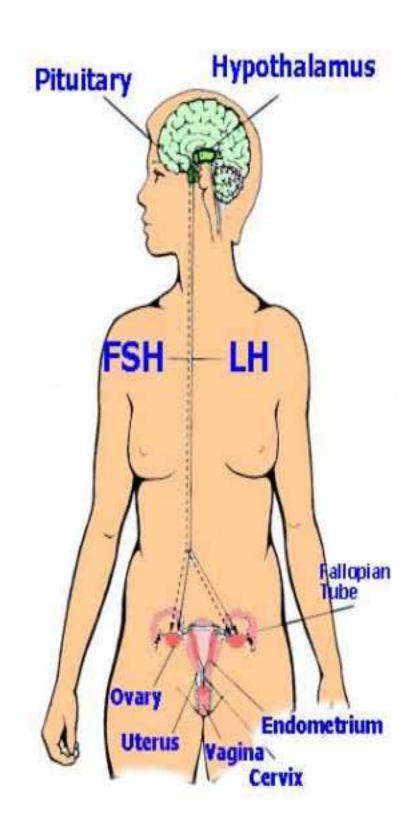
Without the SCN these become arrhythmic



SCN reads duration of pineal melatonin

Drives brain control of ovulation

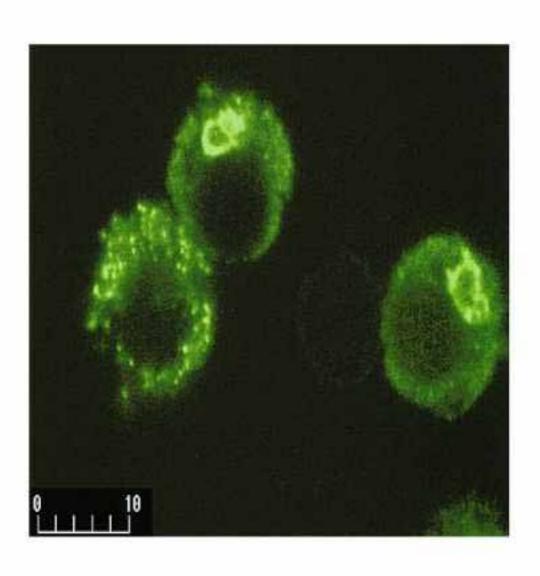




SCN reads duration of pineal melatonin

Drives brain control of ovulation

Also controls prolactin release

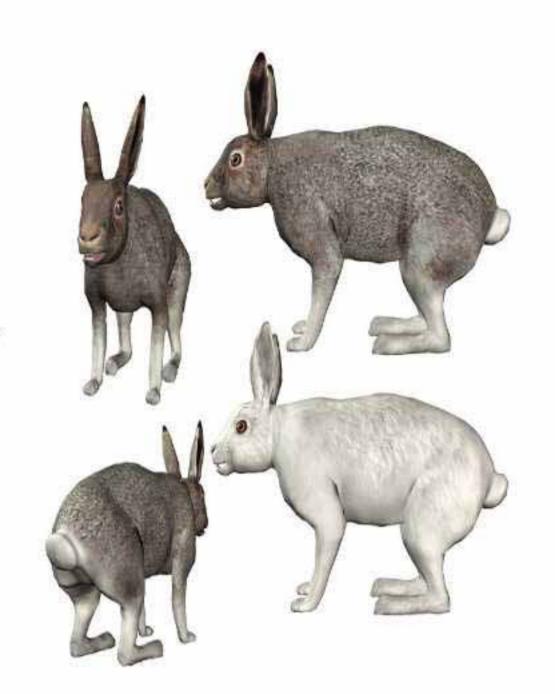


SCN reads duration of pineal melatonin

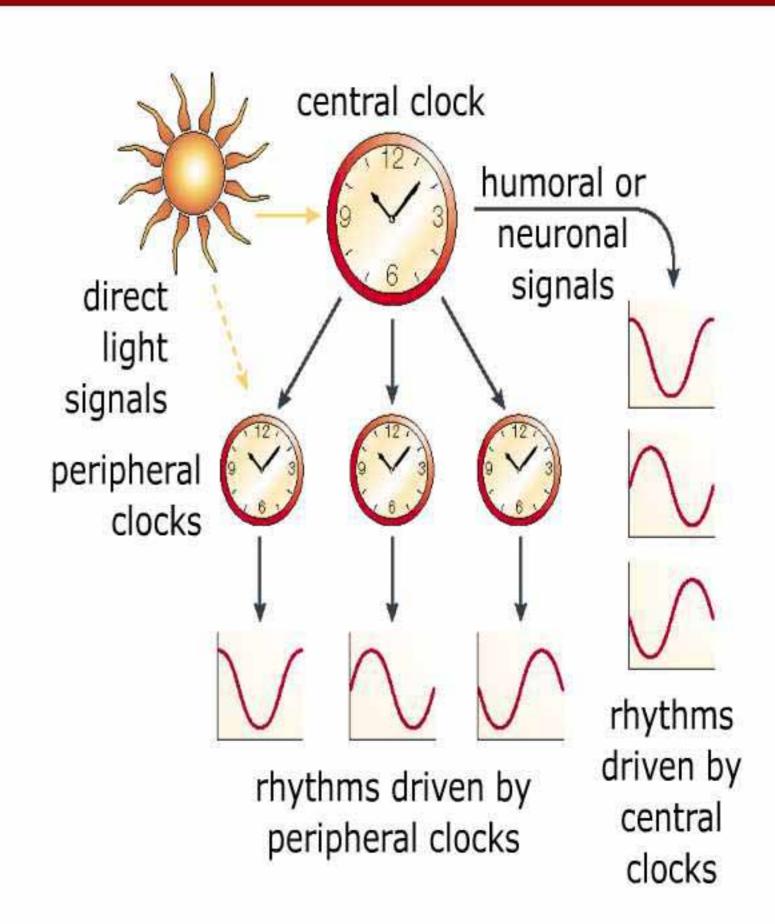
Drives brain control of ovulation

Also controls prolactin release

Affects food intake, metabolic rate, winter coat length and colour



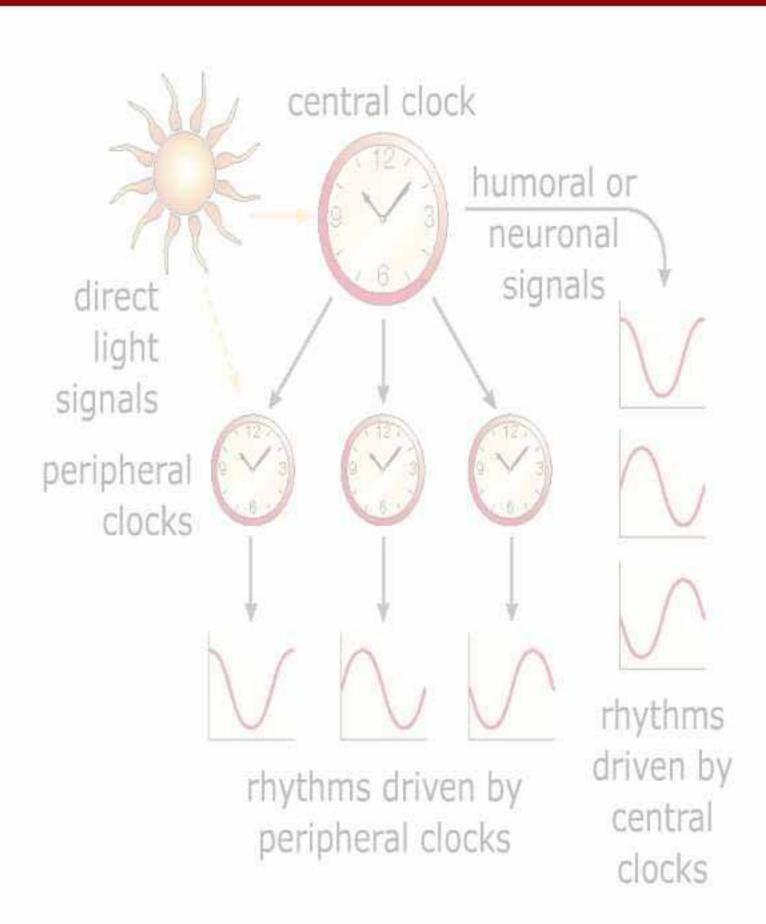
Is the SCN the body's master clock?



## Where?

Is the SCN the body's master clock?

Not completely



## Where?

Is the SCN the body's master clock?

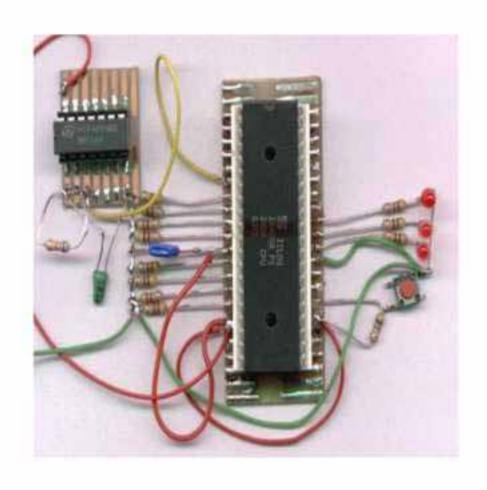
Not completely

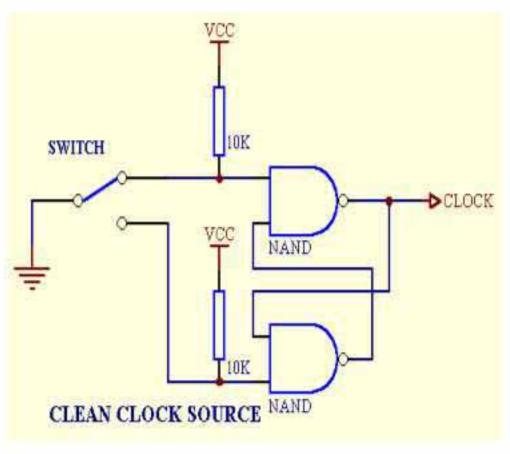




It is more like a democratically elected government than a dictatorship

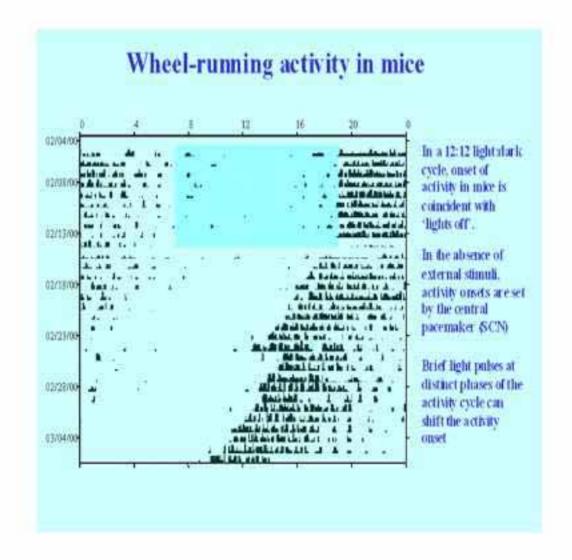
Central requirements are an input, an oscillator and an output





Central requirements are an input, an oscillator and an output

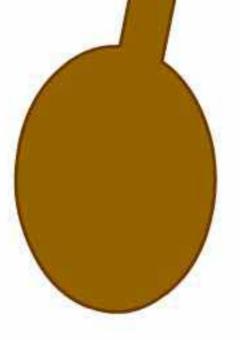
Circadian clocks need a 24h oscillation period



Central requirements are an input, an oscillator and an output

Circadian clocks need a 24h oscillation period

Pendulums usually oscillate at 1 cycle per second



Computer clocks can oscillate at 10,000,000,000 (10<sup>10</sup>) cycles per second

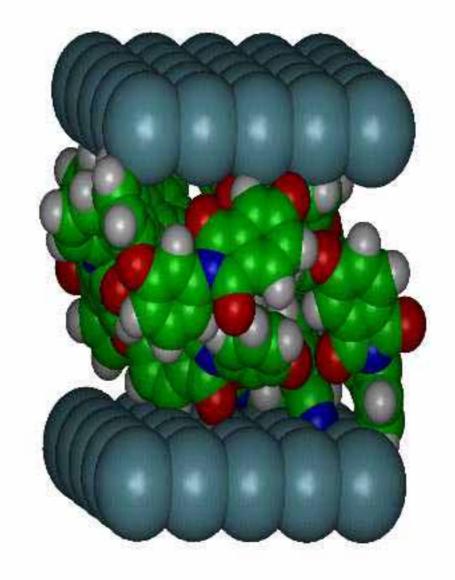


Computer clocks can oscillate at 10,000,000,000 (10<sup>10</sup>) cycles per second

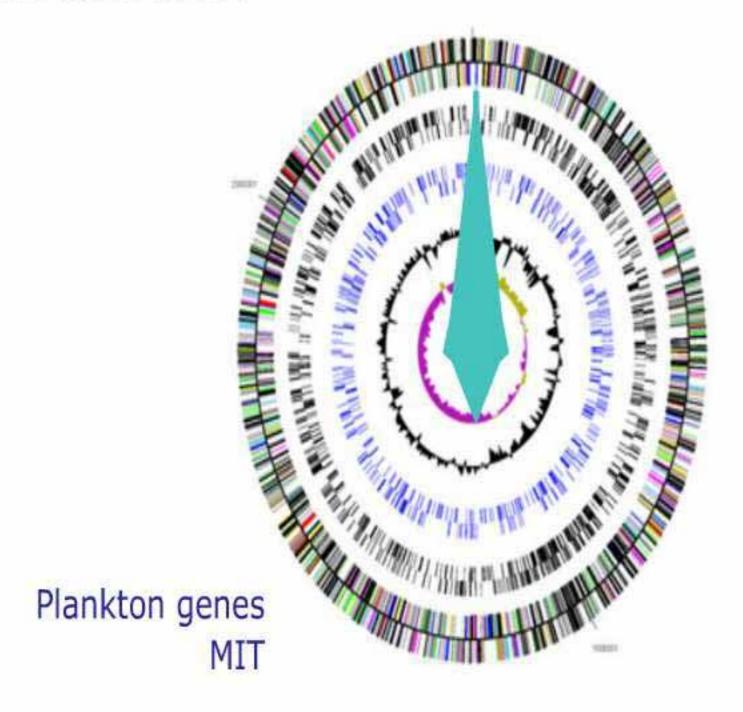
Atoms oscillate at 10,000,000,000,000,000 (10<sup>16</sup>)

cycles per second





What does a biological oscillator involving genes and proteins look like?



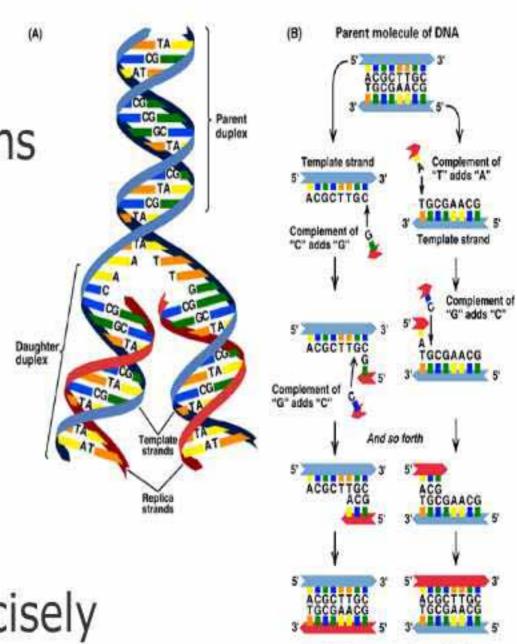
What does a biological oscillator involving genes and proteins look like?

Building blocks are genes and proteins

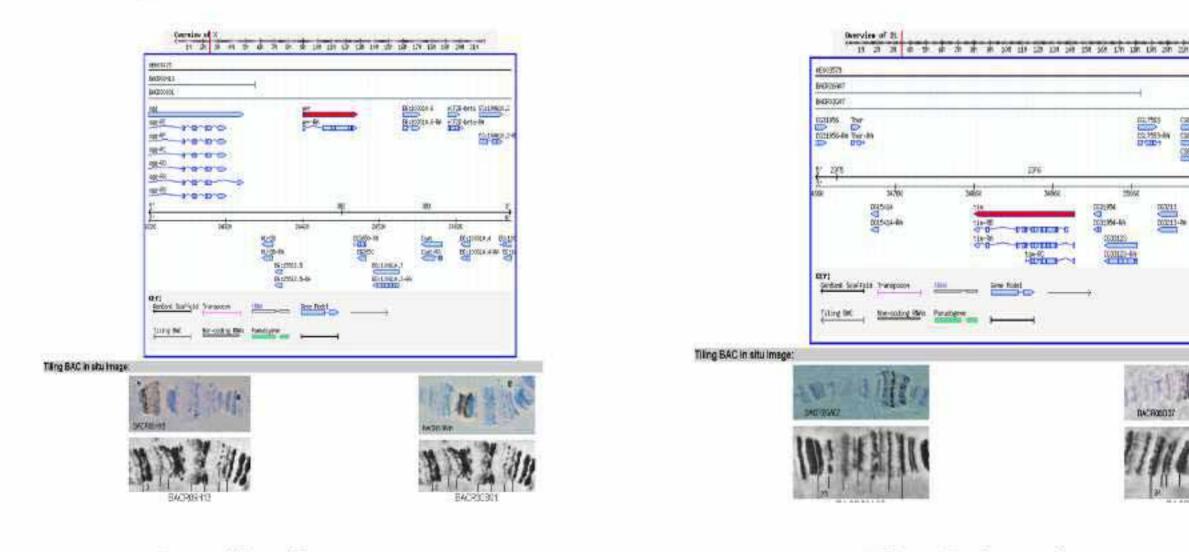
Gene transcription

- Protein translation
- Protein dimerisation and binding
- Protein degradation
- FEEDBACK LOOPS

Each of these molecular steps is precisely temporally controlled (several hours for each)



The first clock genes were identified in drosophila mutagenesis screens

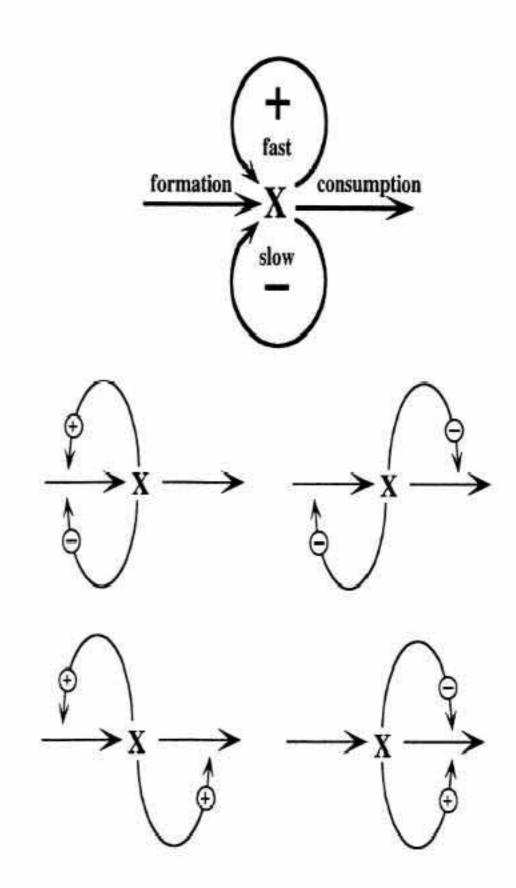


Per(iod) gene

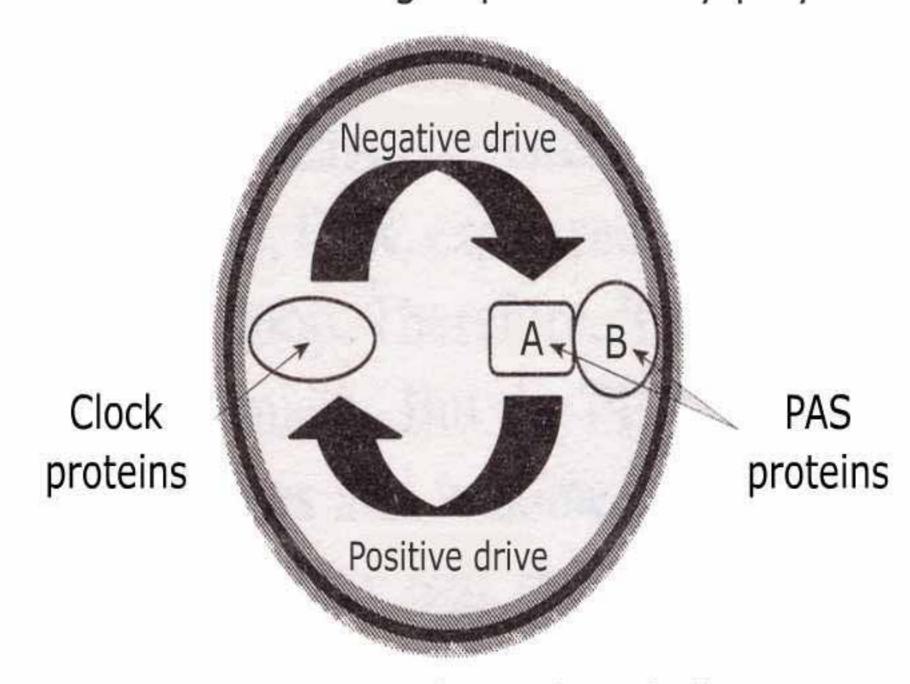
Tim(eless) gene

The bad news is that the molecular cogs and operators of biological clocks differ

The good news is that they all seem to function with a positive and a negative feedback autoregulatory loop

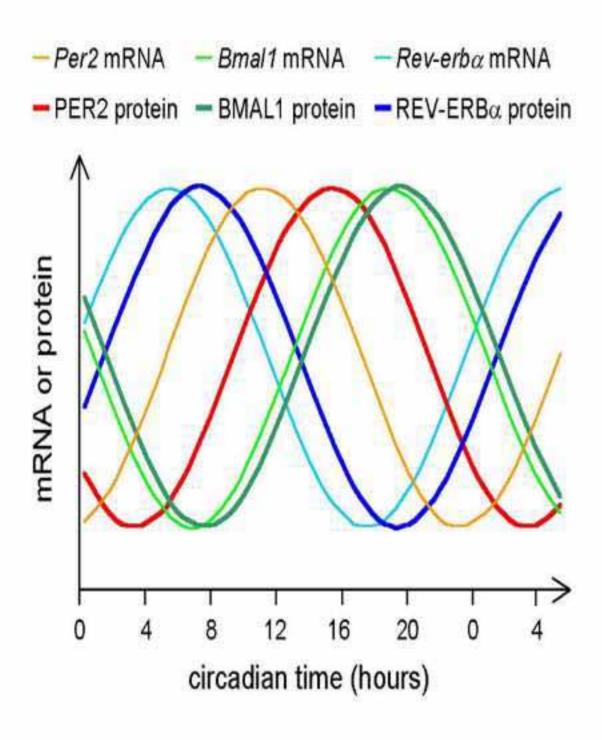


We now have a reasonable grasp of the key players



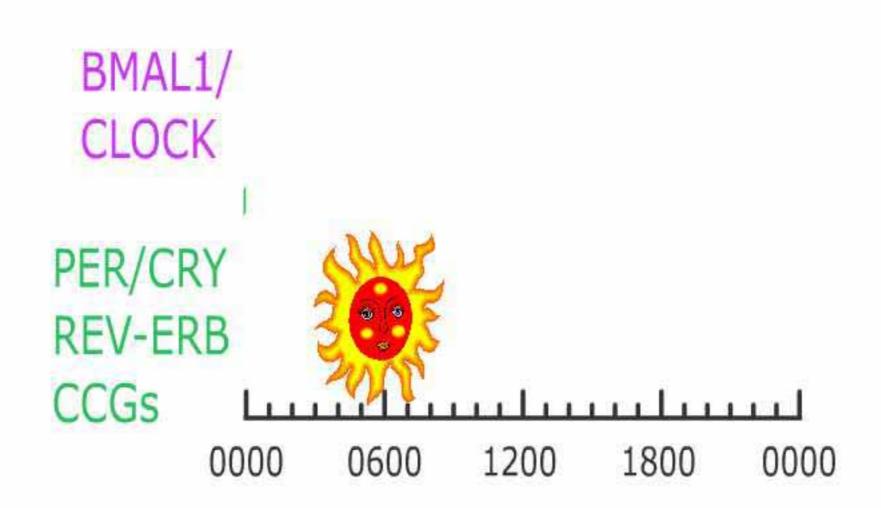
Conceptual circadian clock

### The mouse SCN clock

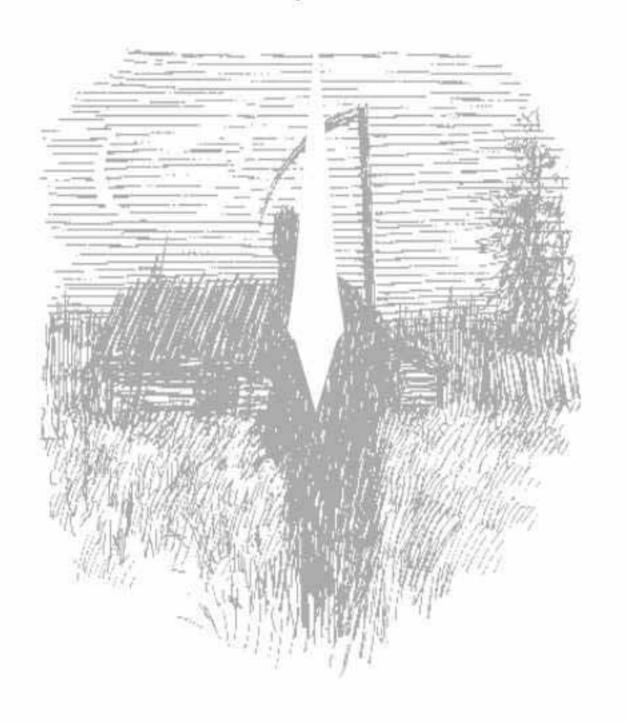




Entraining effects of light



Malfunctioning biological clocks will at best make life miserable and at worst may even lead to death



Jet lag - the problem

Human evolution did not cater for travel by air or even by boat

Every 1 hour time zone we cross takes 1 day for our clocks to reset

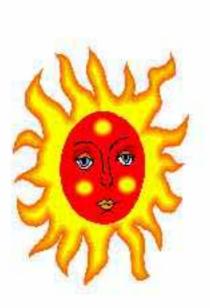
It takes 5 days to recover from a trip from London to New York

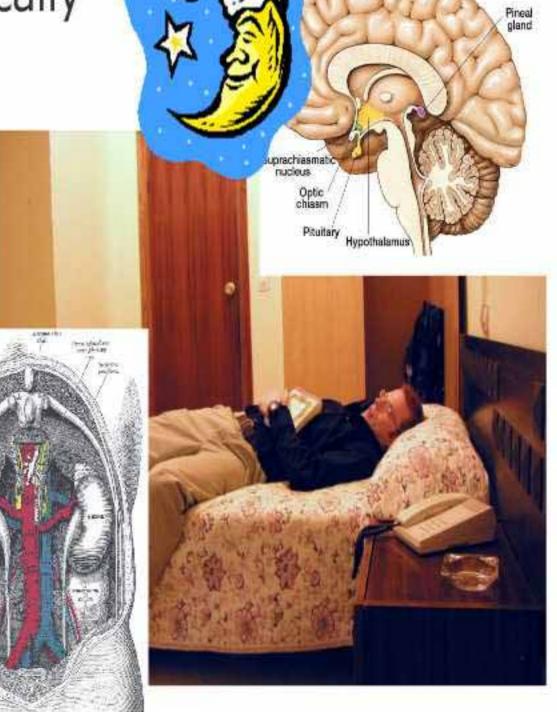
Why can symptoms get dramatically worse 2-3 days after travelling?



Why can symptoms get dramatically worse 2-3 days after travelling?

Central and peripheral clocks recover at different rates and start opposing one another





Why is it worse travelling east than west?

Our clocks seem to adjust better after a prolonged day than a shortened one



# Jet-lag - possible ways to alleviate problems

Keep on home time and don't expose yourself to daylight at the wrong time

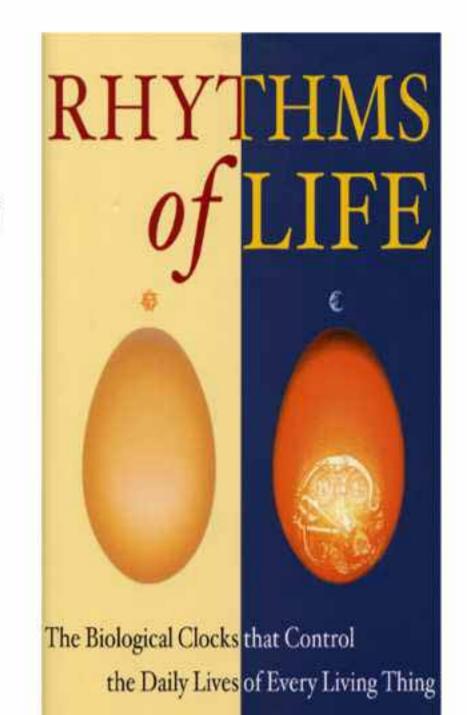


# Jet-lag - possible ways to alleviate problems

Speed up adaptation to time zone changes by controlled exposure to light at different times of day

Foster and Kreitzman (2004)

Prior to body temperature minimum (4 am) light will delay your clocks, and after this it will advance them



### Melatonin

Licensed for use in the USA but not the UK

Reduces jet-lag symptoms if taken at the right time



Our 24/7 society requires that many industries and services continue around the clock



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Our biological clocks can just about cope with a complete shift in our day and night cycles but it is not recommended

Please
No HOT Disturb!
Night Shift Worker's
We Sleep During
the DAY!

Our 24/7 society requires that many industries and services continue around the clock

Our biological clocks can just about cope with a complete shift in our day and night cycles but it is not recommended

It takes a week or so to adapt to a night shift

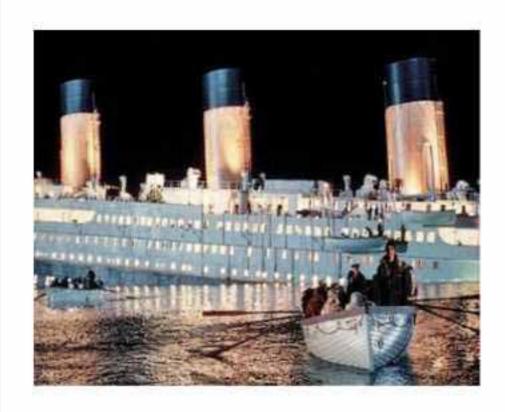


Chopping and changing shift times is a nightmare for our biological clocks and often leads to states of chronic sleep

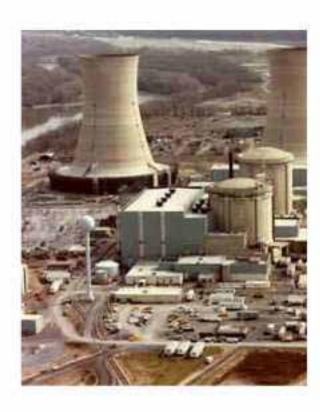
deprivation



What do disasters such as the Titanic, Estonia, Exxon Valdez, Three Mile Island, Chernobyl and Bhopal have in common?







They all occurred at night when workers were on a night shift

Workers on night-shifts have a 20% higher risk of injury than on day shifts



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After four night shifts a worker has a 50% higher risk of a road accident



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After four night shifts a worker has a 50% higher risk of a road accident

Higher risk of cancer and cardiovascular diseases





# Strategies for dealing with shift work

# No agreed best policy on this

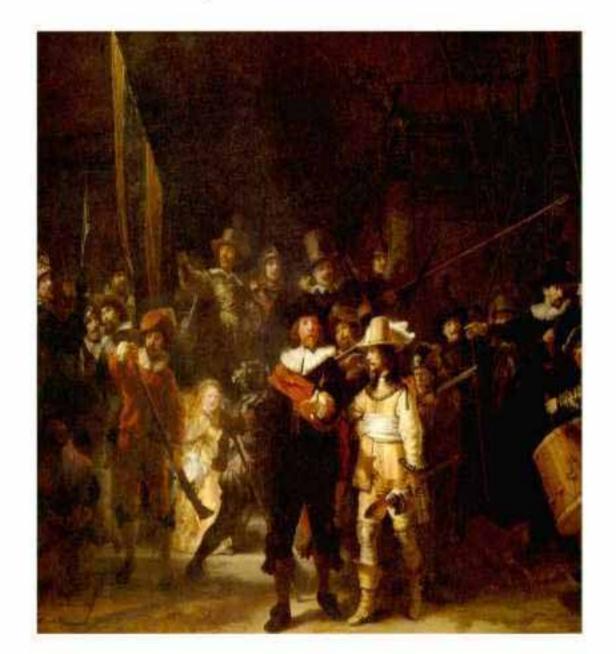


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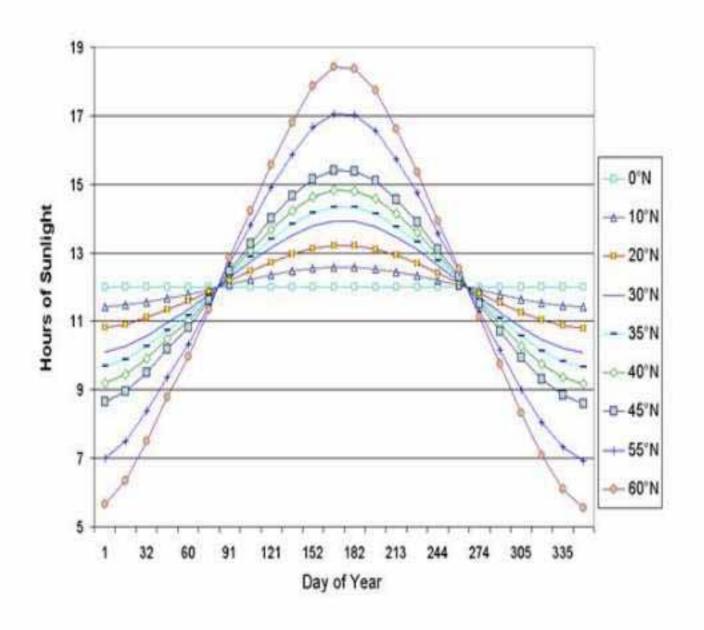
Weekends are a problem however!

Speed of shift changes and length of shifts can make a difference



# Seasonal affective disorder (SAD)

Our human circadian pacemaker can detect seasonal changes in day length



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Our human circadian pacemaker can detect seasonal changes in day length

This can have subtle effects on our behaviours, emotions, physiology and biochemistry

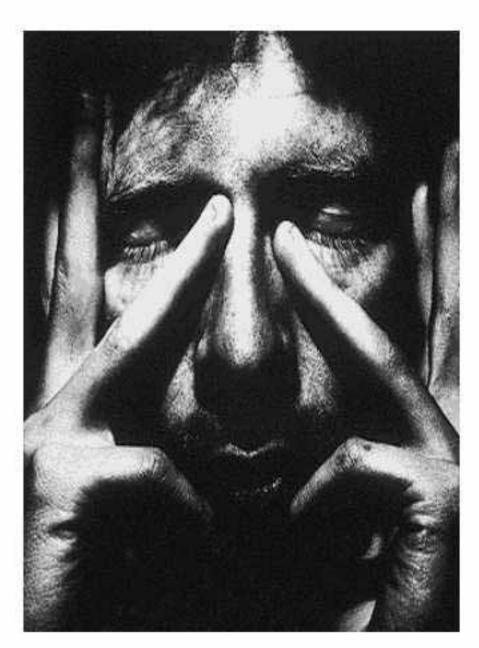


# Seasonal affective disorder (SAD)

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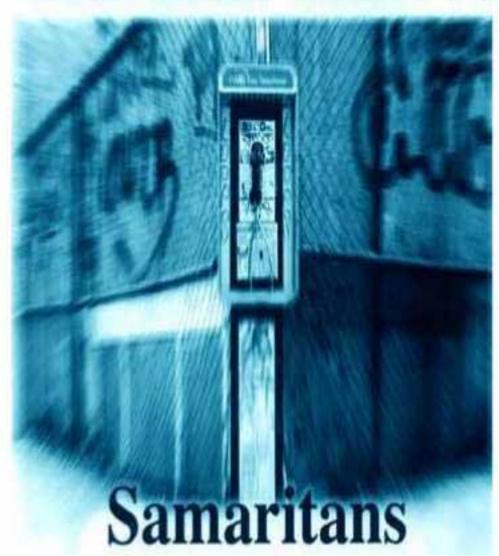
This can have subtle effects on our behaviours, emotions, physiology and biochemistry

For 3% of people in the UK, and more in Northern latitudes, shortening days cause a profound depression



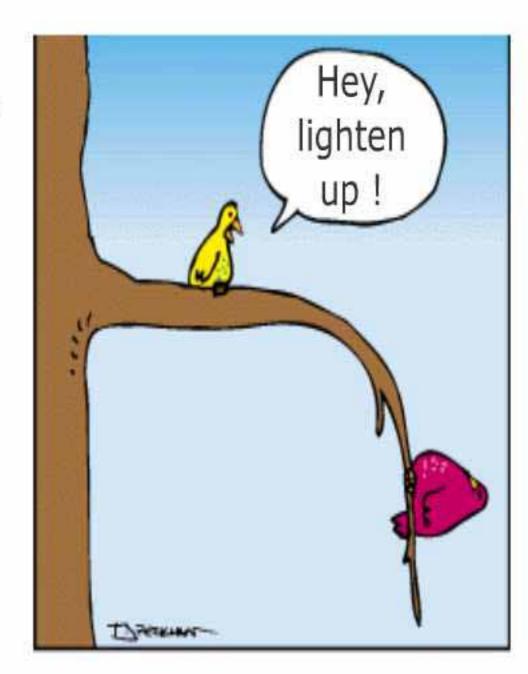
Individuals become seriously depressed, socially withdrawn, lethargic and even suicidal





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They crave carbohydrates and may put on 5-15 kilograms in weight



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They crave carbohydrates and may put on 5-15 kilograms in weight

Symptoms largely disappear with lengthening days

It resembles hibernating animal species - lethargy and weight gain

Ancestral signal to become inactive or migrate south?



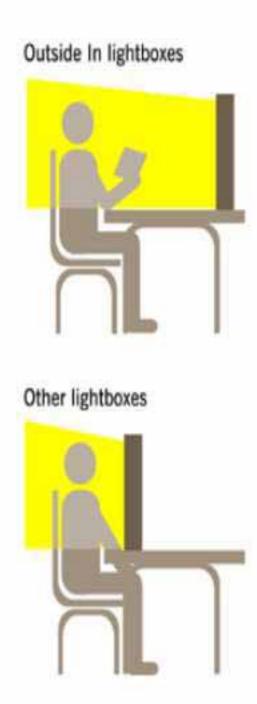


#### Treatments for SAD

Exposure to high intensity light sources that resemble normal day light







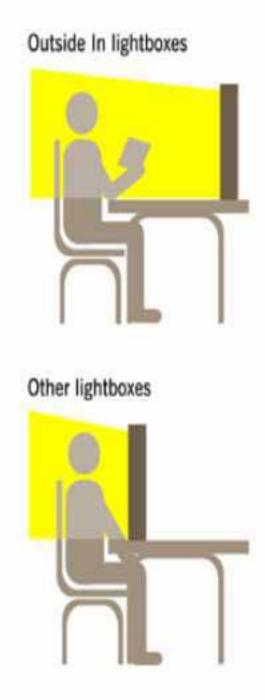
#### Treatments for SAD

Exposure to high intensity light sources that resemble normal day light

2500 lux (a cloudy day) for around 45 minutes between 3.30 and 8 am







Old Father Time makes our biological time clocks erratic

Sleep duration is less and we spend less time in deep stages

Almost all other rhythms become less pronounced

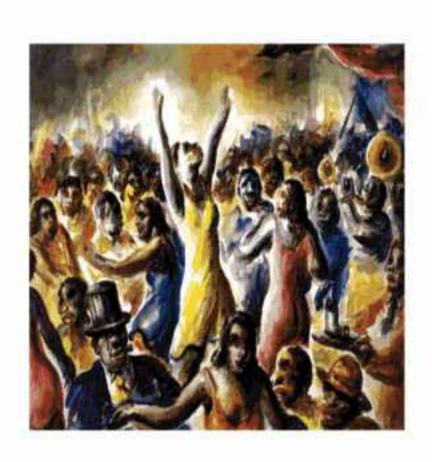
We really are less affected by the ups and downs of life



Potential remedies:

Don't mess your clocks about too much when you are young

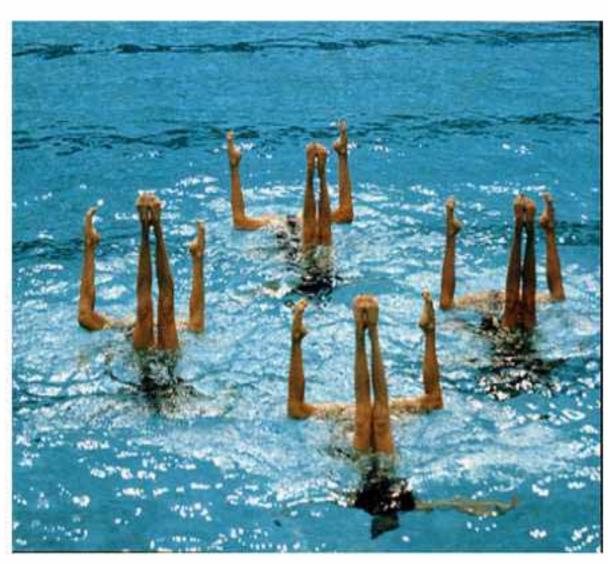




Potential remedies:

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Try to keep to regular lifestyle schedules



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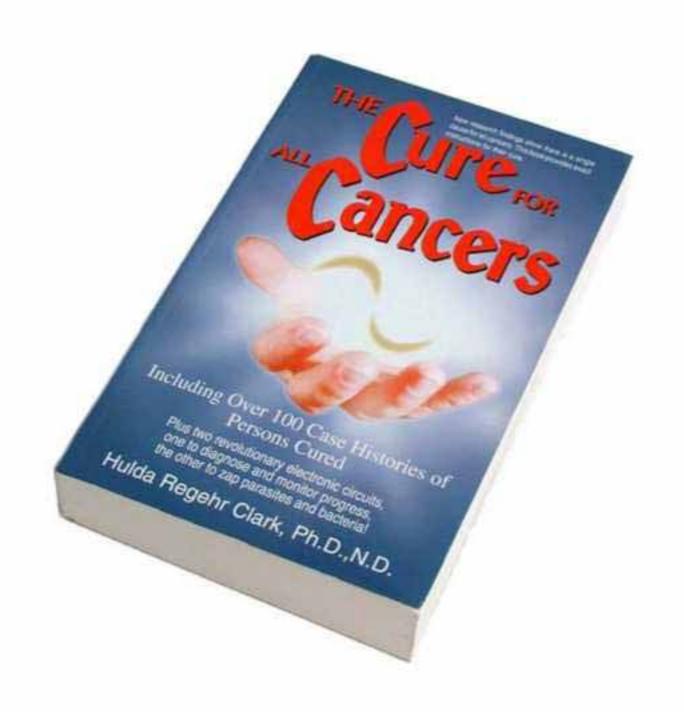
Try to keep to regular lifestyle schedules

Melatonin?

Get new clocks!

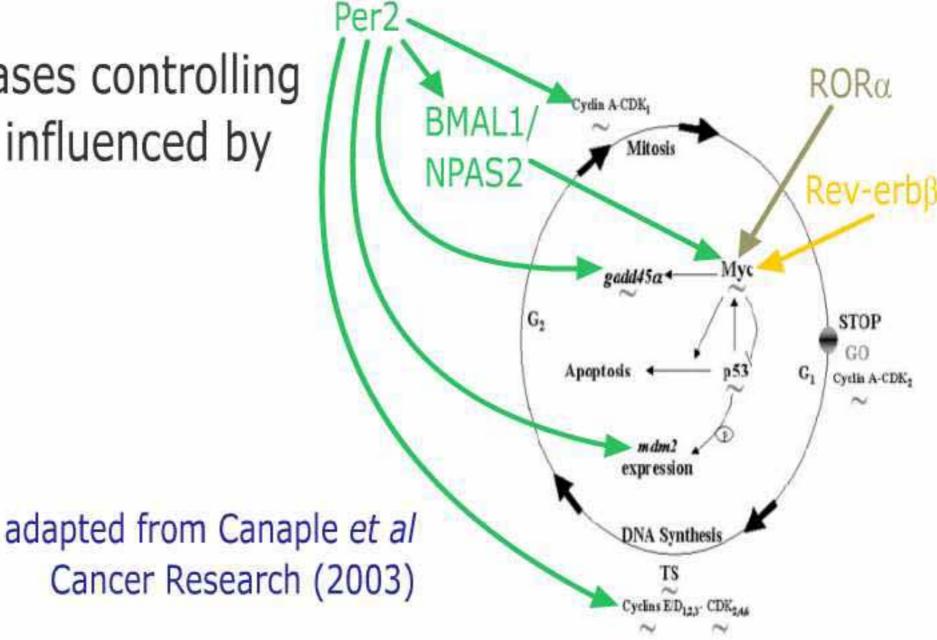


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All cell cycle phases controlling cell division are influenced by clock genes



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Tumours in mice without a brain clock grow more quickly

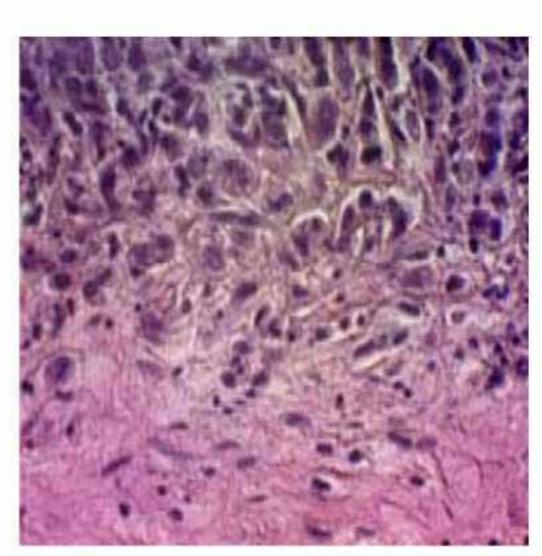


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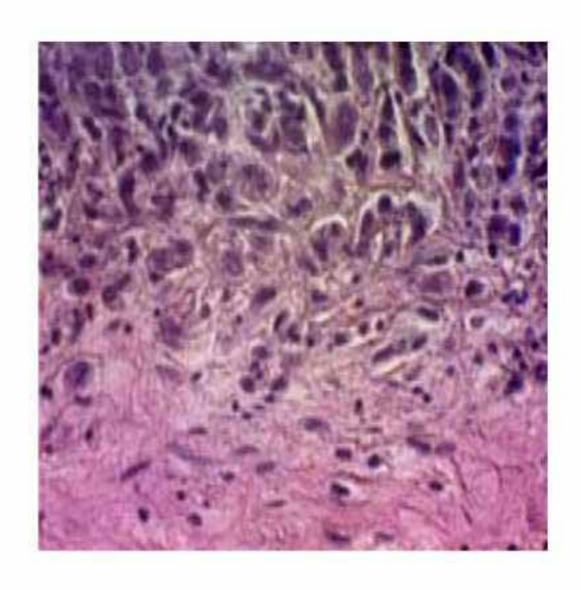
All cell cycle phases controlling cell division are influenced by clock genes

Tumours in mice without a brain clock grow more quickly

Mice lacking the per2 clock gene develop more spontaneous tumours

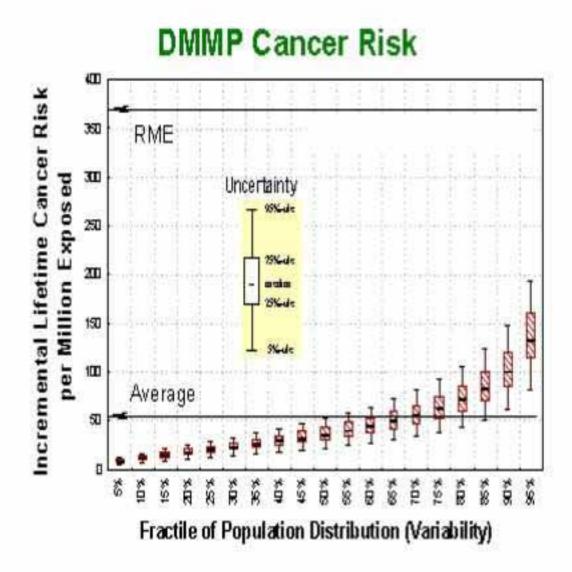


Conclusion: our biological clocks and clock genes are tumour suppressors



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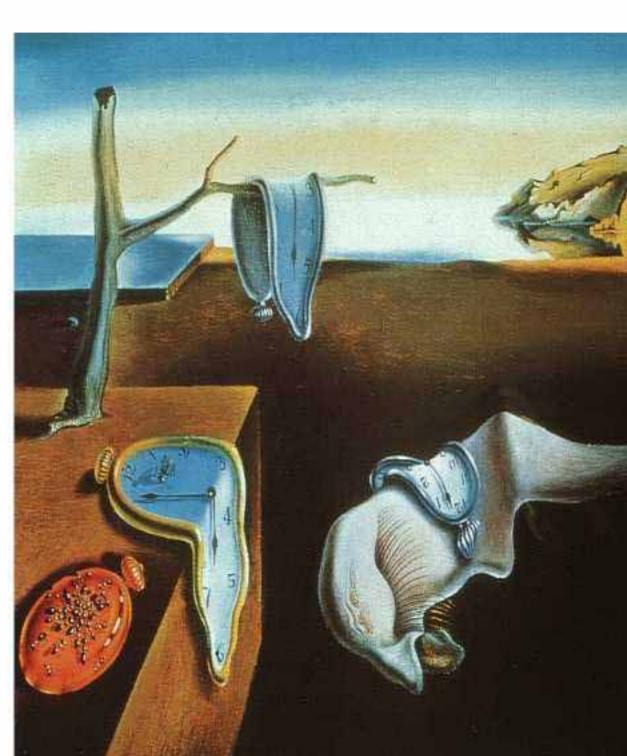
This may be why frequent long-distance travel and shift work increase cancer risk



Conclusion: our biological clocks and clock genes are tumour suppressors

This may be why frequent long-distance travel and shift work increase cancer risk

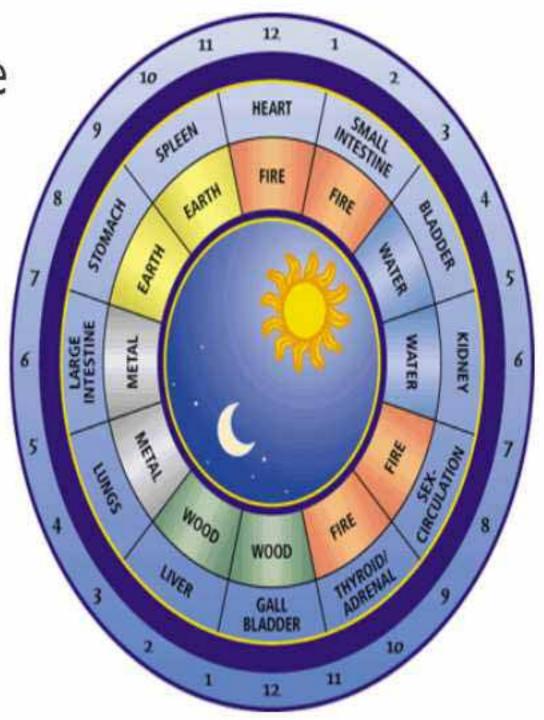
Cancer cells also have clocks but these are out of phase with normal cells



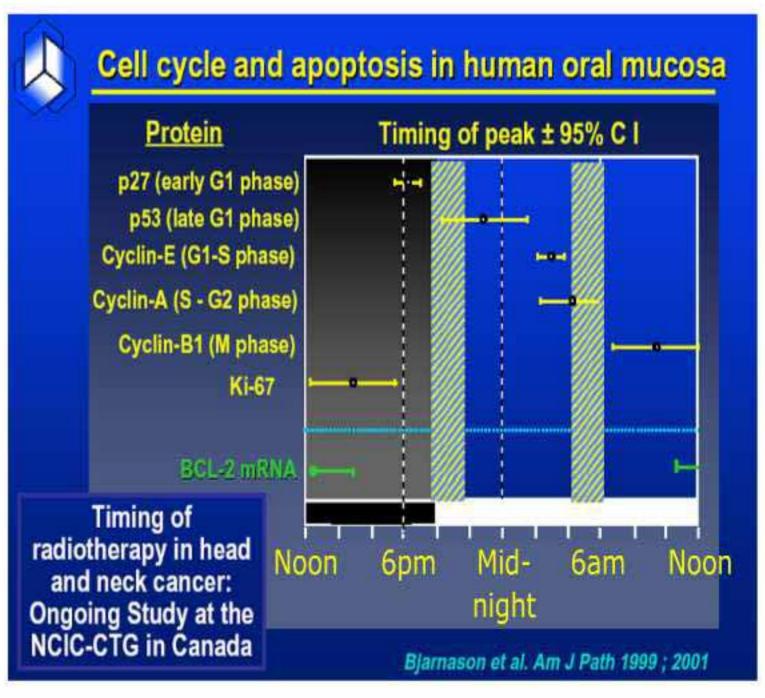
## It's time for your medicine dear

Chronotherapy

When you give a medicine may be almost as important as what it is

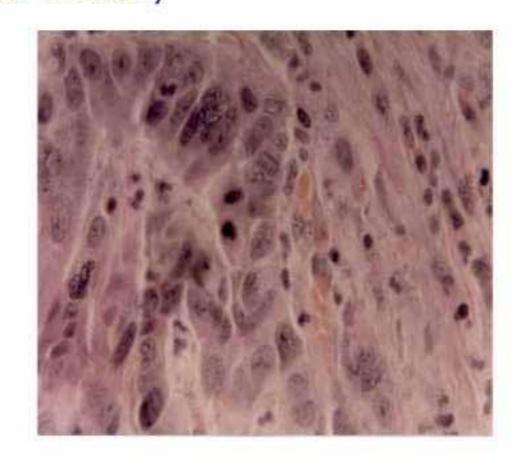


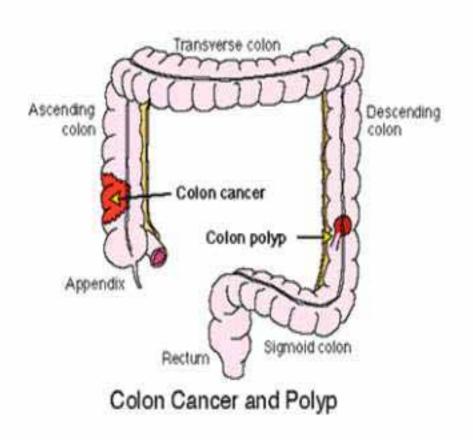
Timing doses to coincide with vulnerable S and G2 phases of dividing cancer cells



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Colon cancer - 40% higher dose, 3-fold increase in >50% tumour shrinkage (Levi et al 2001)





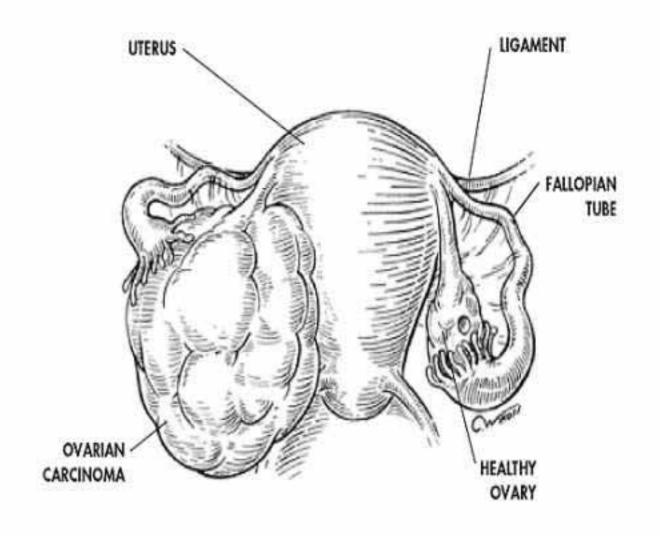
Timing doses to coincide with vulnerable S and G2 phases of dividing cancer cells

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(Levi et al 2001)

Improved effectiveness for treating ovarian cancer (Hrushesky 1985)



#### Cancers with seasonal patterns

- cervical, breast and testicular

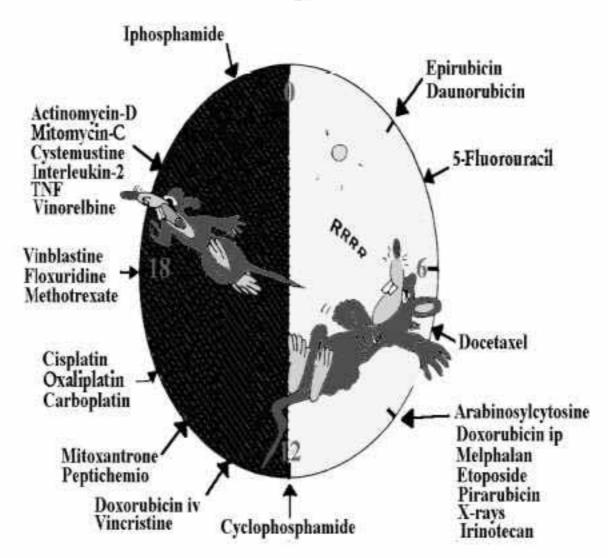




#### Cancers with seasonal patterns

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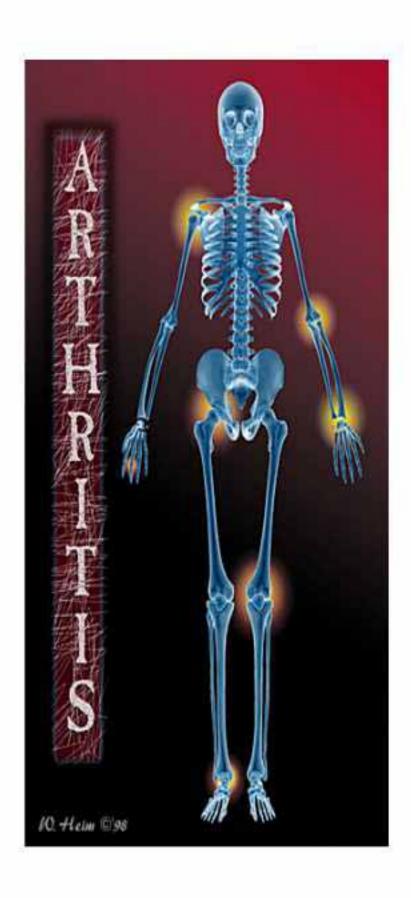
## Optimal periods for screening and treatment regimes?



## Other possibilities

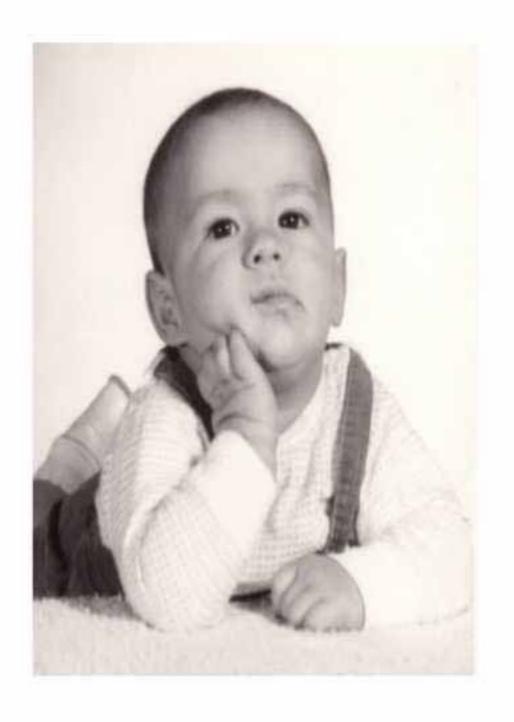
Rheumatoid arthritis (peaks around 6-8am)

Osteoarthritis (peaks around 4-6pm)



# Time perception





The birds and the bees are champion time users rather than

sex symbols



The birds and the bees are champion time users rather than sex symbols

Bees for breakfast (August Forel 1910)



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Dancing bees (von Frisch 1950)

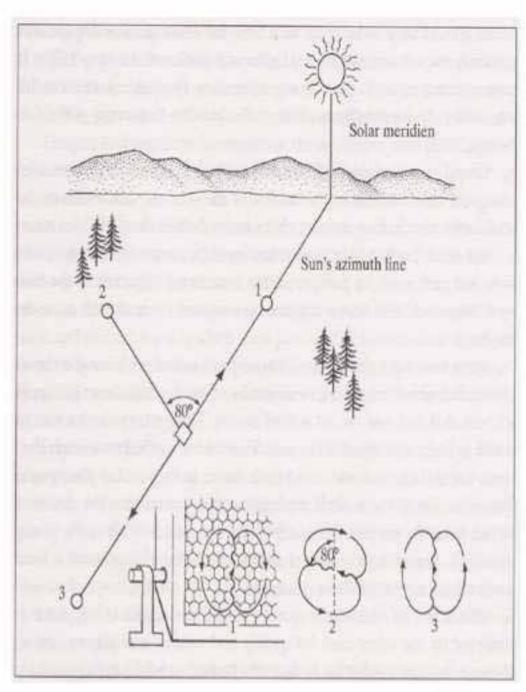


The birds and the bees are champion time users rather than sex symbols

Bees for breakfast (August Forel 1910)

Dancing bees (von Frisch 1950)

Compute time by movements of the sun (15°/hour)



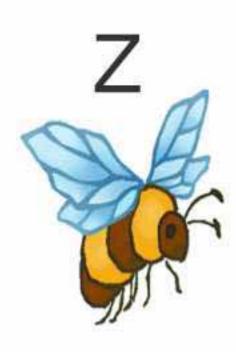
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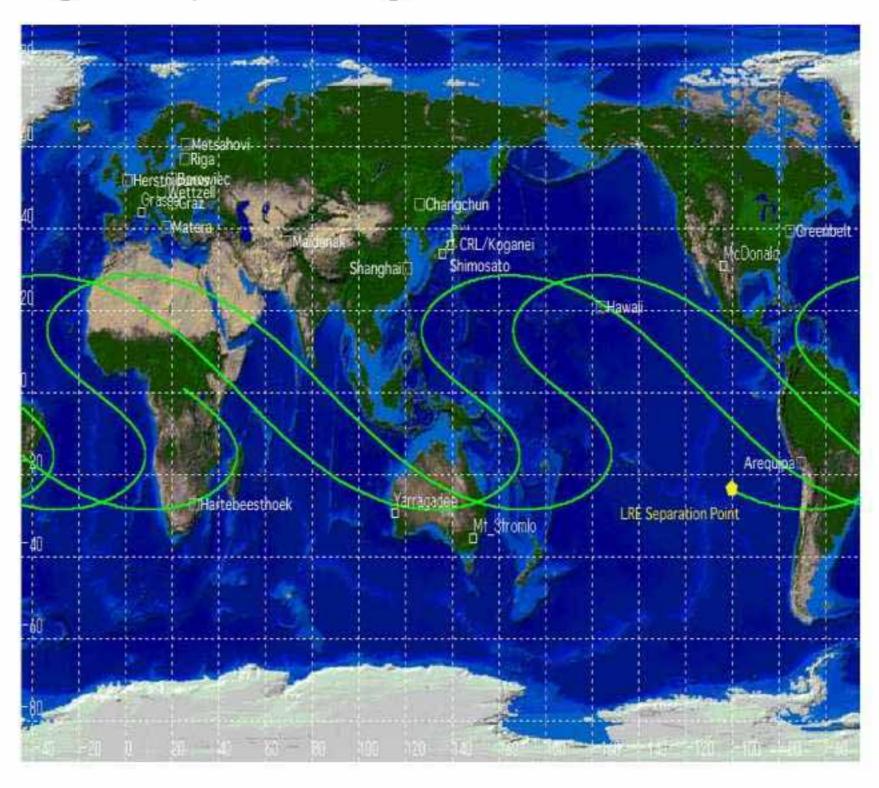
Dancing bees (von Frisch 1950)

Compute time by movements of the sun (15°/hour)

The problems of curfew!



## Biological global positioning device

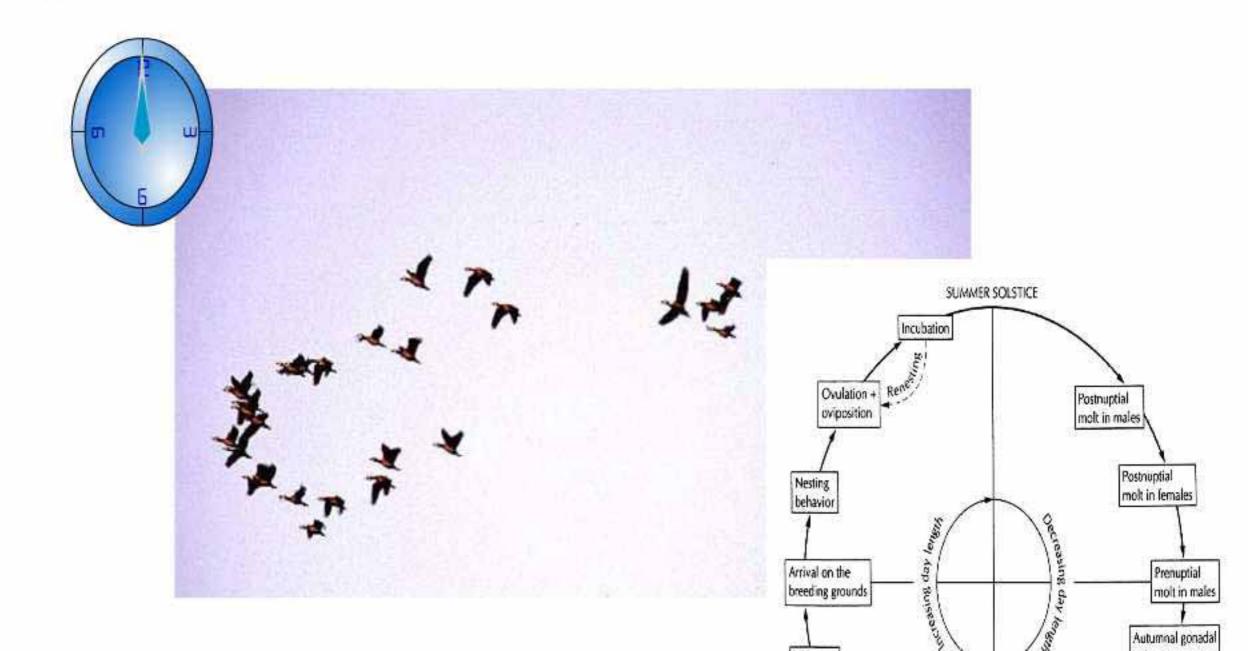


Migrating birds are also champion time users

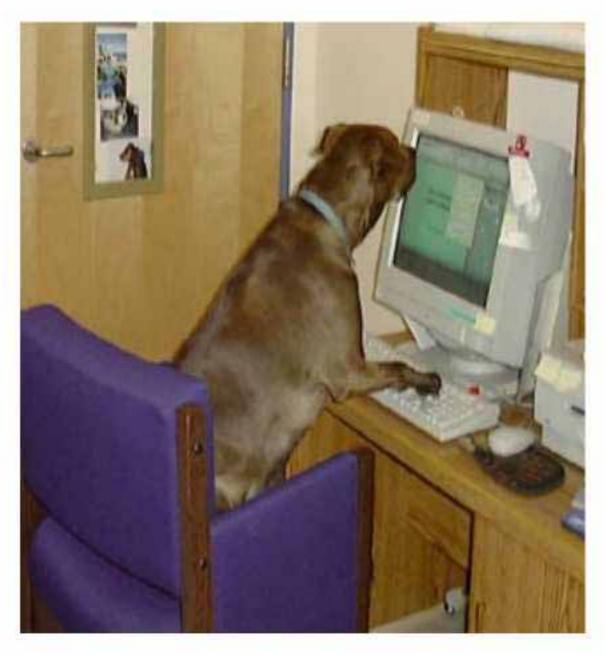


Migrating birds are also champion time users

They have two clocks - a circadian and a circannual one



Many other animals can be trained to perform time interval tasks



Many other animals can be trained to perform time interval tasks

Dogs and cats waiting for owners

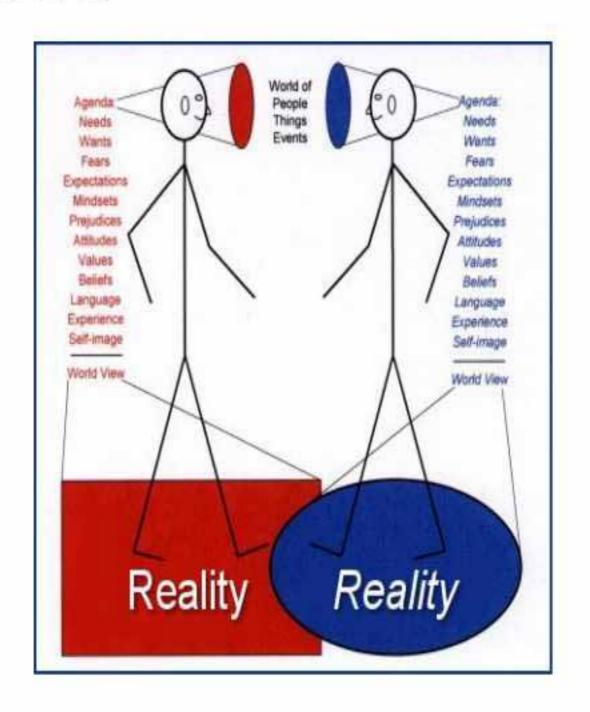


#### Time perception and consciousness

Time use to guide behaviour may not equate to having a conscious perception or a concept of it

We conceive time egocentrically

We put present, past or future events in the context of our own personal experience



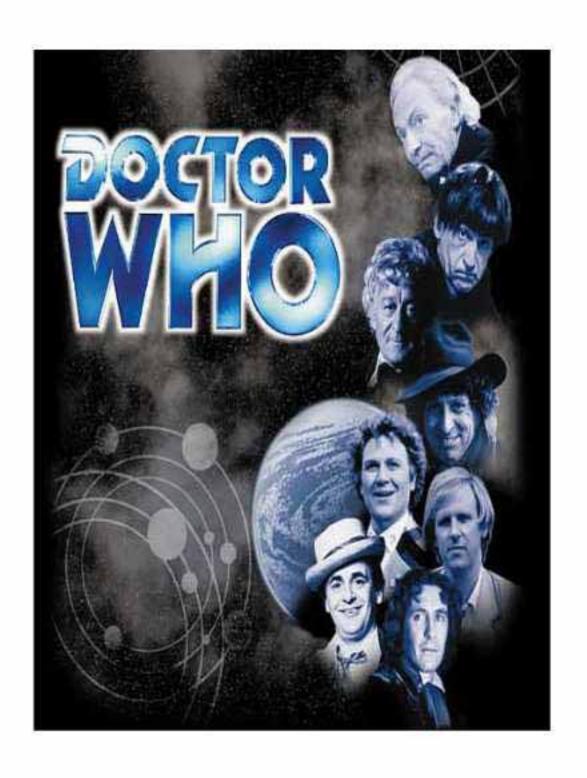
#### Time perception and consciousness

It requires self-consciousness to conceive of time in this way

This is in short supply in other species

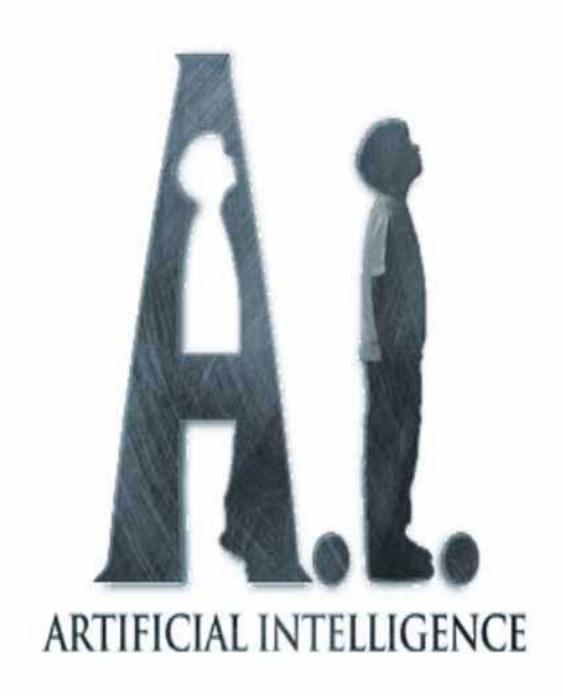


We are all mental time travellers



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Claimed to be unique to humans



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Develops in parallel with self-awareness (2 - 4 years)

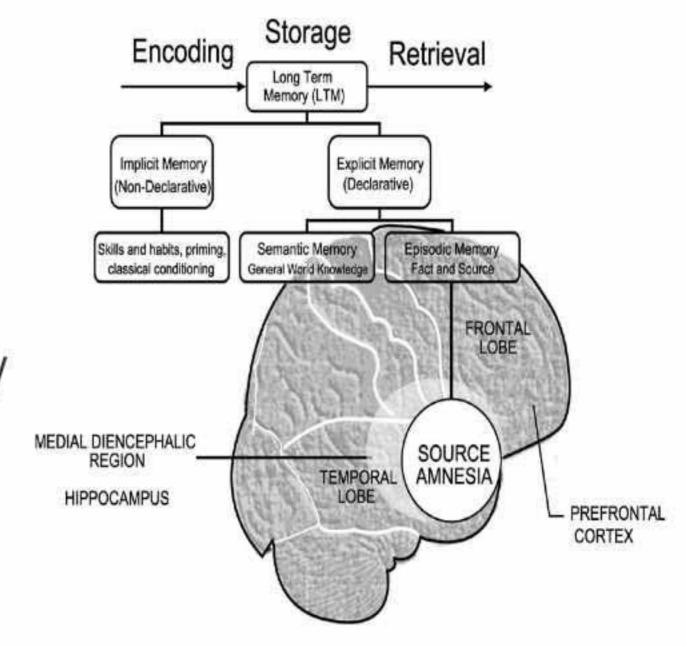


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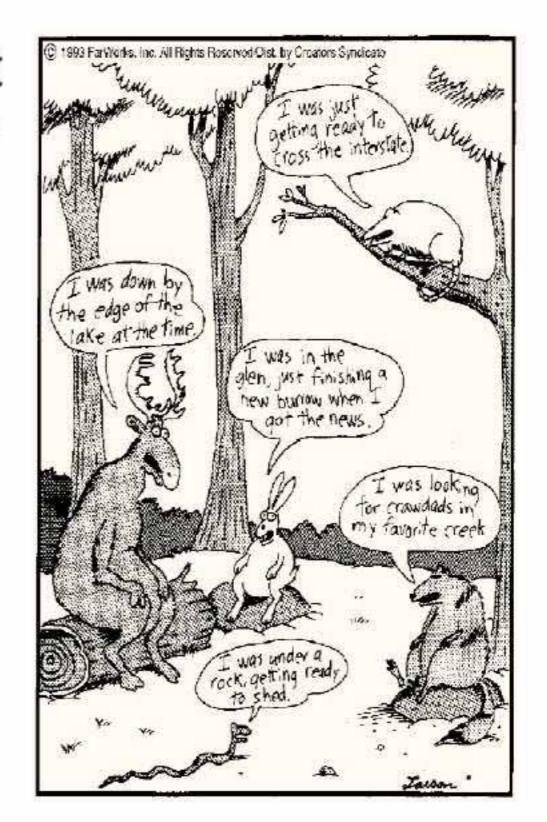
Integration of what, when and where - episodic memory



Can animals really mentally revisit the past or see the possible future?

'All forest animals, to this very day, remember exactly where they were and what they were doing when they heard that Bambi's mother had been shot'

Gary Larson



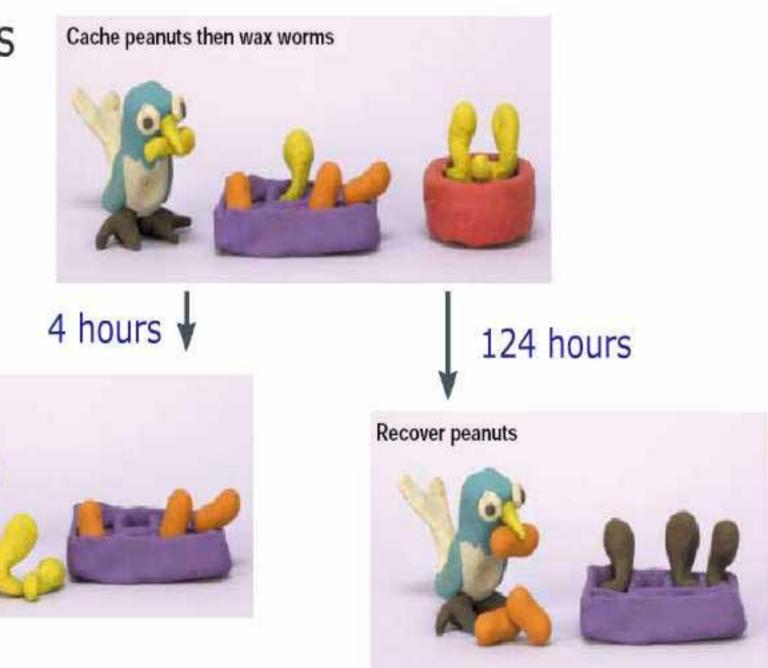
# Enter the Western Scrub Jay



# The best things in life don't last long

Recover worms

Wax worms vs peanuts



The best things in life don't last long

Wax worms vs peanuts

We tend to rely on sell-by dates



The best things in life don't last long

Wax worms vs peanuts

We tend to rely on sell-by dates

Recent experiments on celebrity humans may not!





## Can scrub-jays see into the future?

Caching



In private



3 hours







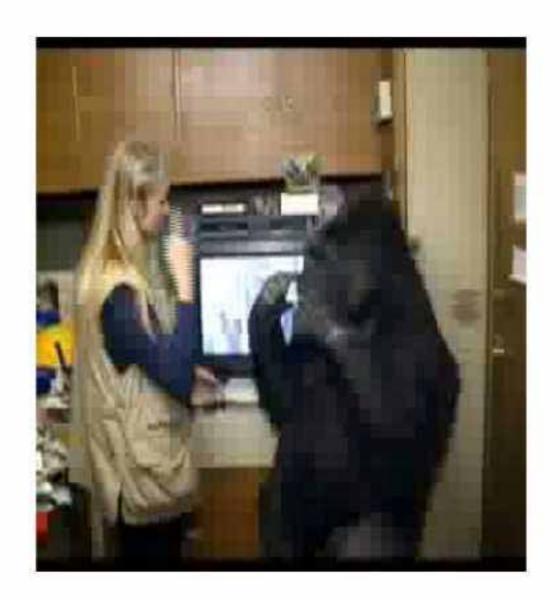
In private



Can scrub-jays see into the future?

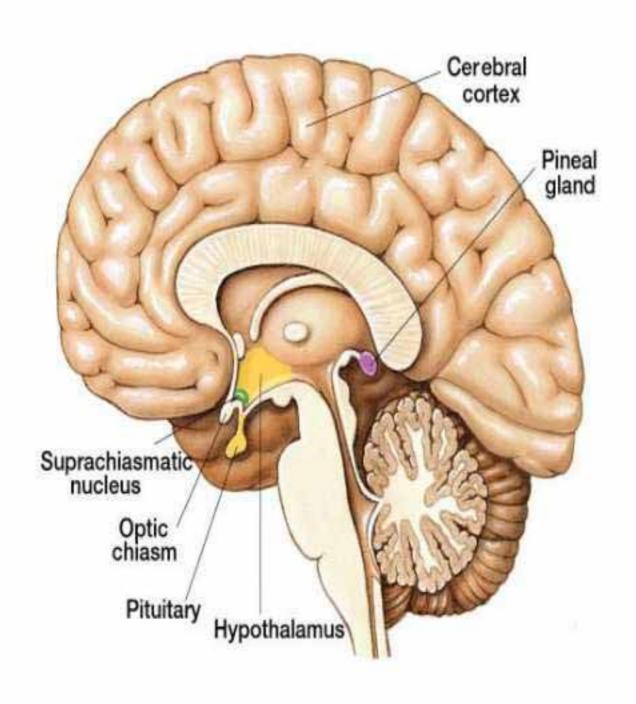
Still may not need to do mental time travel to use time cues

Language apes may hold the key



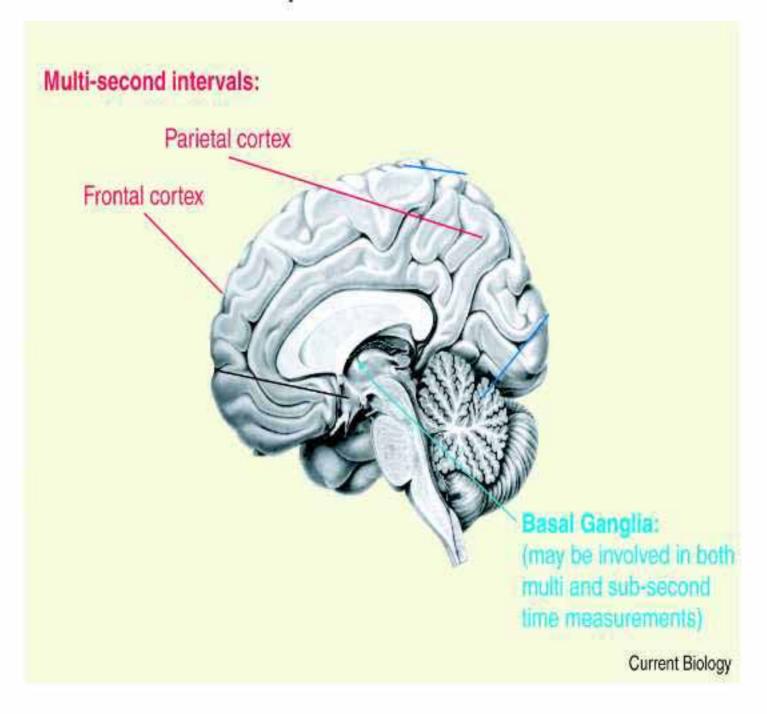
## Time perception and the brain

The suprachiasmatic nucleus may not be important



#### Time perception and the brain

Timing involving durations of many seconds or longer tend to involve the frontal and parietal cortex



# Time perception and the brain

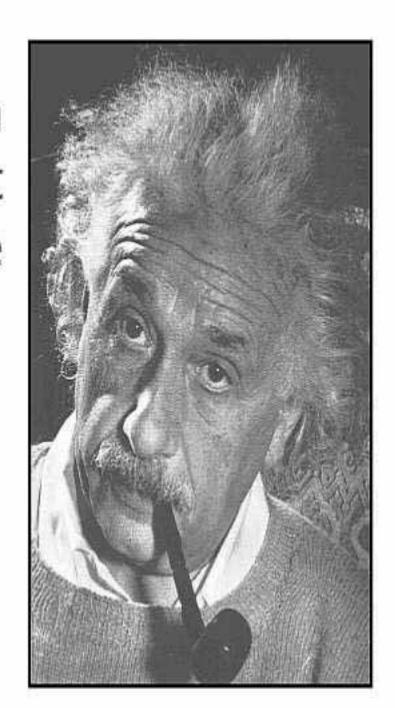
The case of KC Tulving et al (1988)



Time perception is highly subjective and relative to your situation

'When you are courting a nice girl an hour seems like a second. When you sit on a red-hot cinder a second seems like an hour. That's relativity'

(Albert Einstein)



Time really is experienced faster when you're having fun





Time really is experienced faster when you're having fun

Time really is slowed down when you are bored and depressed



Time really is experienced faster when you're having fun

Time really is slowed down when you are bored and depressed

Time perception is distorted in Schizophrenia, Depression and ADHD

It is slowed down by high and sped up by low body temperature

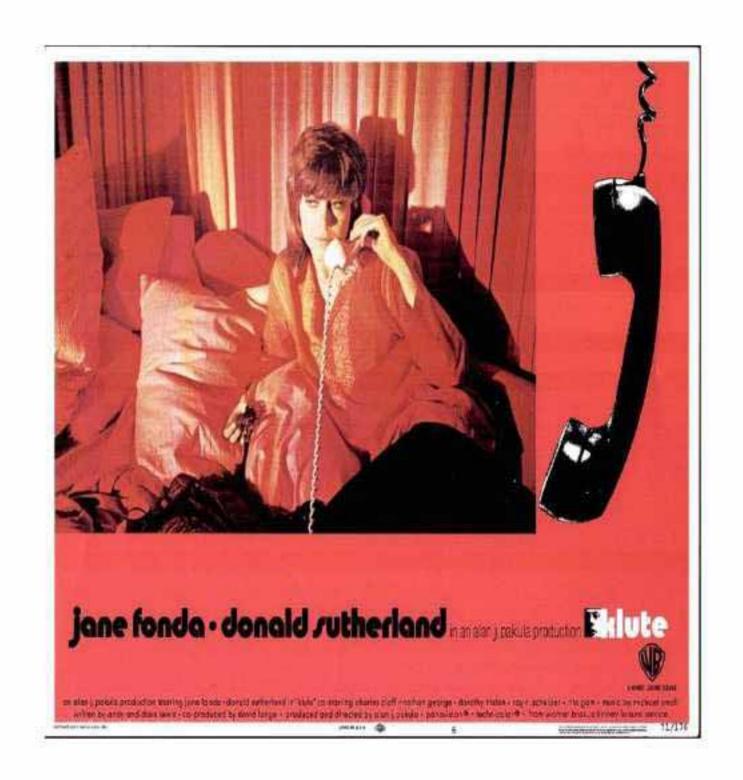
Men underestimate short periods of time (<1 min) and overestimate long ones

Women overestimate short periods of time (<1 min) and underestimate long ones

'I have been on a calendar but never on time' Marilyn Monroe

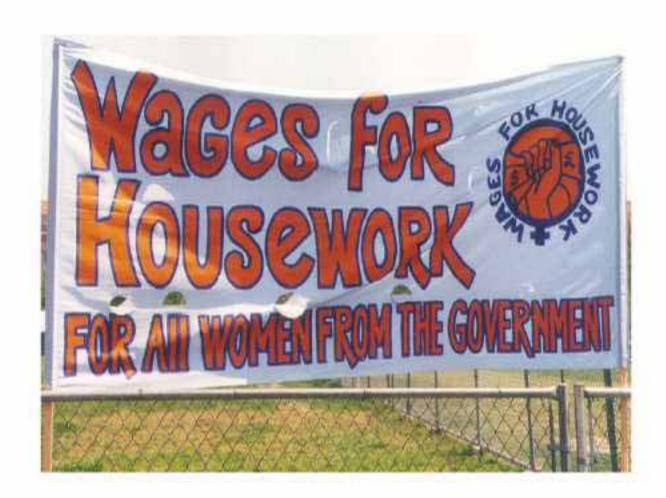


It may be a functional adaptation to male sex duration



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This could explain why men think they can do in a minute what women do in one hour

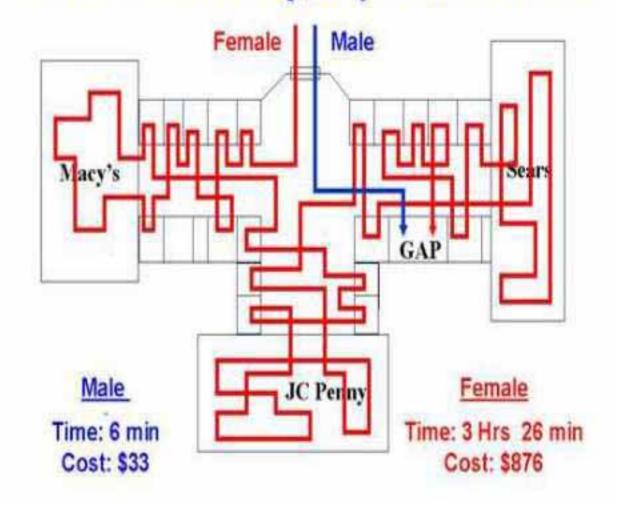


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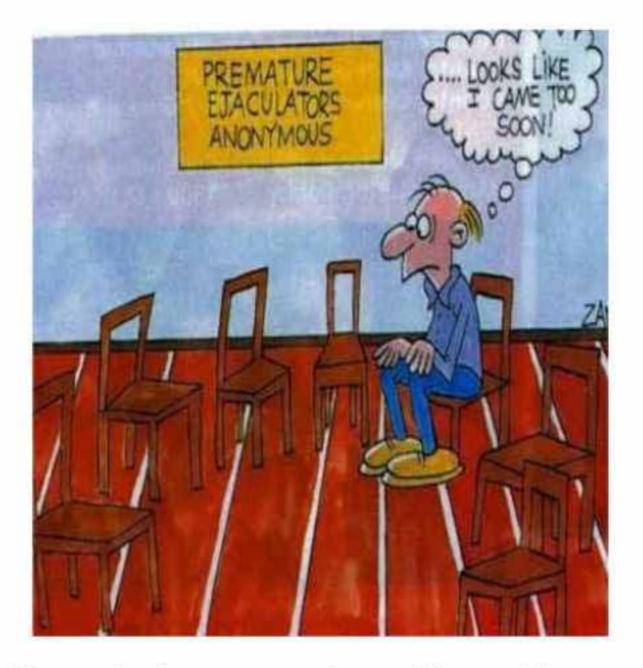
This could explain why men think they can do in a minute what women do in one hour

Or why men think women are later than they really are

#### Mission: Go to Gap, Buy a Pair of Pants



If women think that men take too little time over sex.....



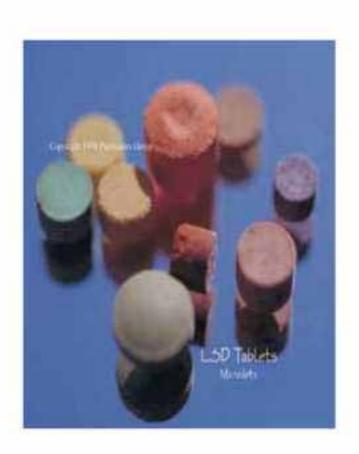
Men know that they take even less time than women think !

# Drugs and time perception

Cannabis, opium and LSD slow down time perception of time





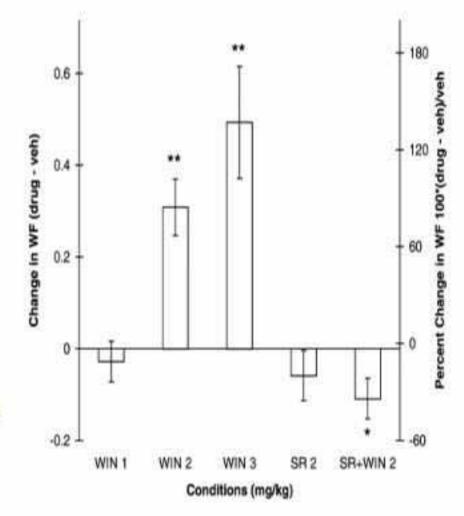


## Drugs and time perception

Cannabis, opium and LSD slow down time perception of time

Even rats on cannabis can no longer discriminate short from

long intervals



Crystal *et al* Behavioural Brain Research (2003)

## Drugs and time perception

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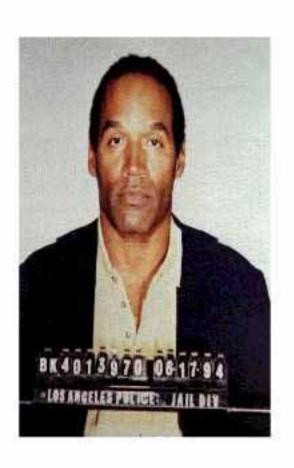
Even rats on cannabis can no longer discriminate short from

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Giving up smoking makes time drag

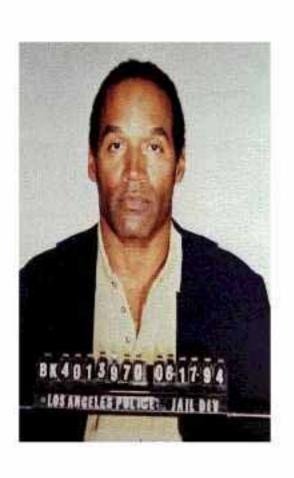


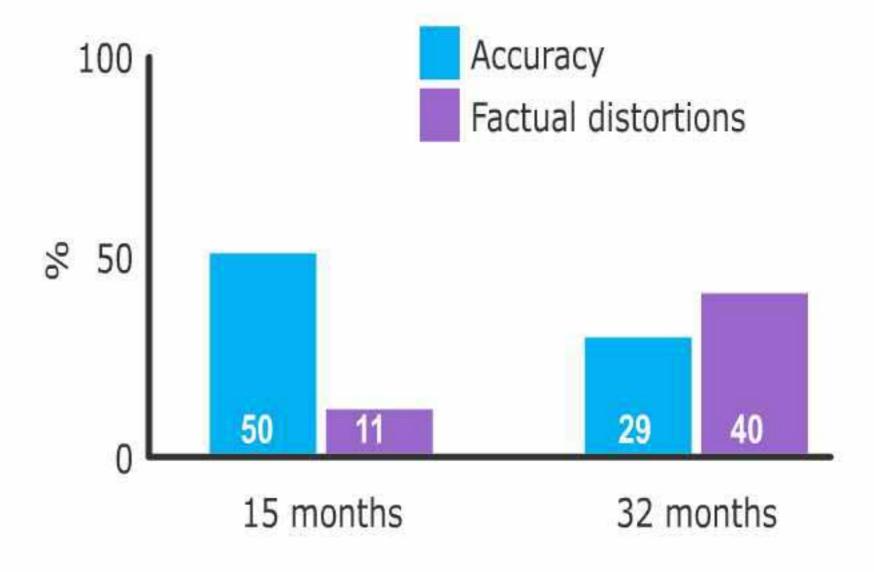
Time distorts accurate memory for events Schmolk et al (2000)





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Time distorts accurate memory for events Schmolk et al (2000)

Don't rely on brains as long-term accurate repositories of events

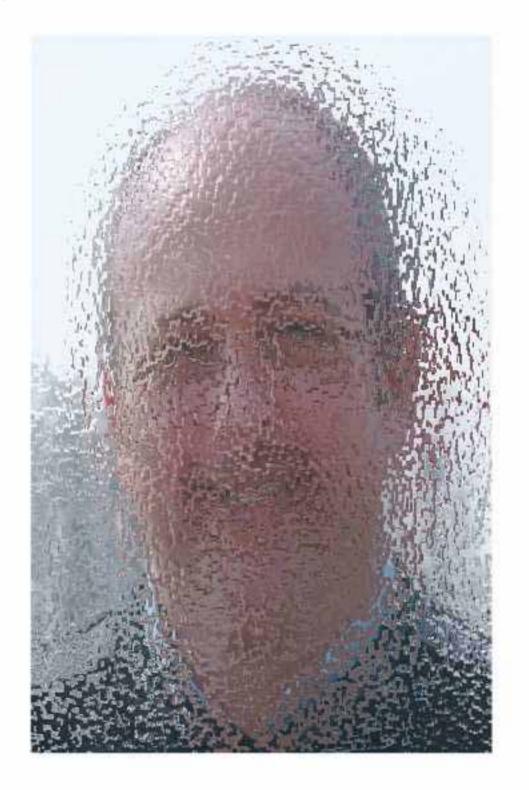




Why does the brain distort memory for events?

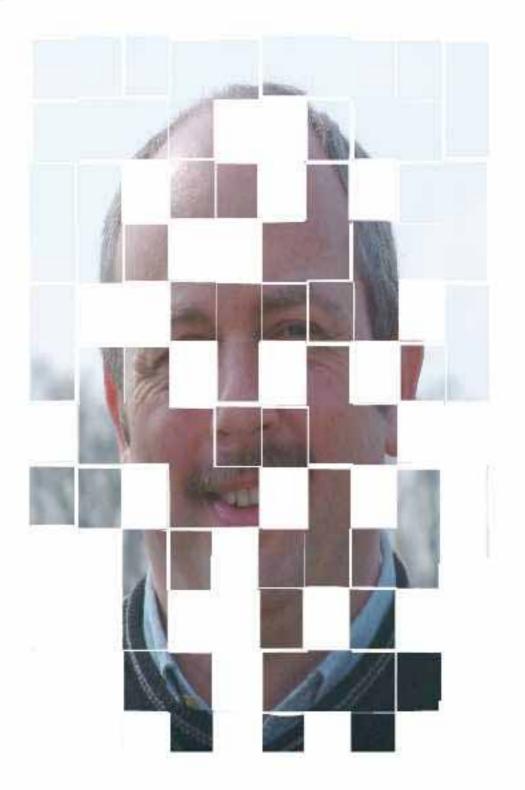


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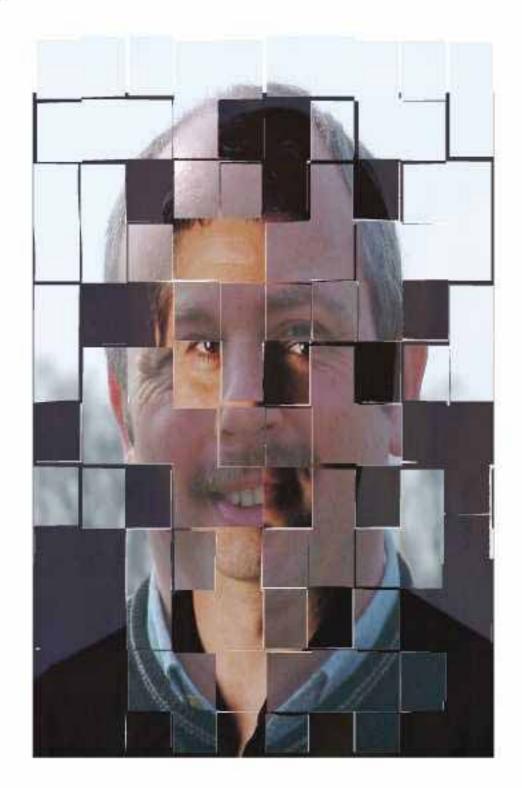
Active recall only brings back snippets of information

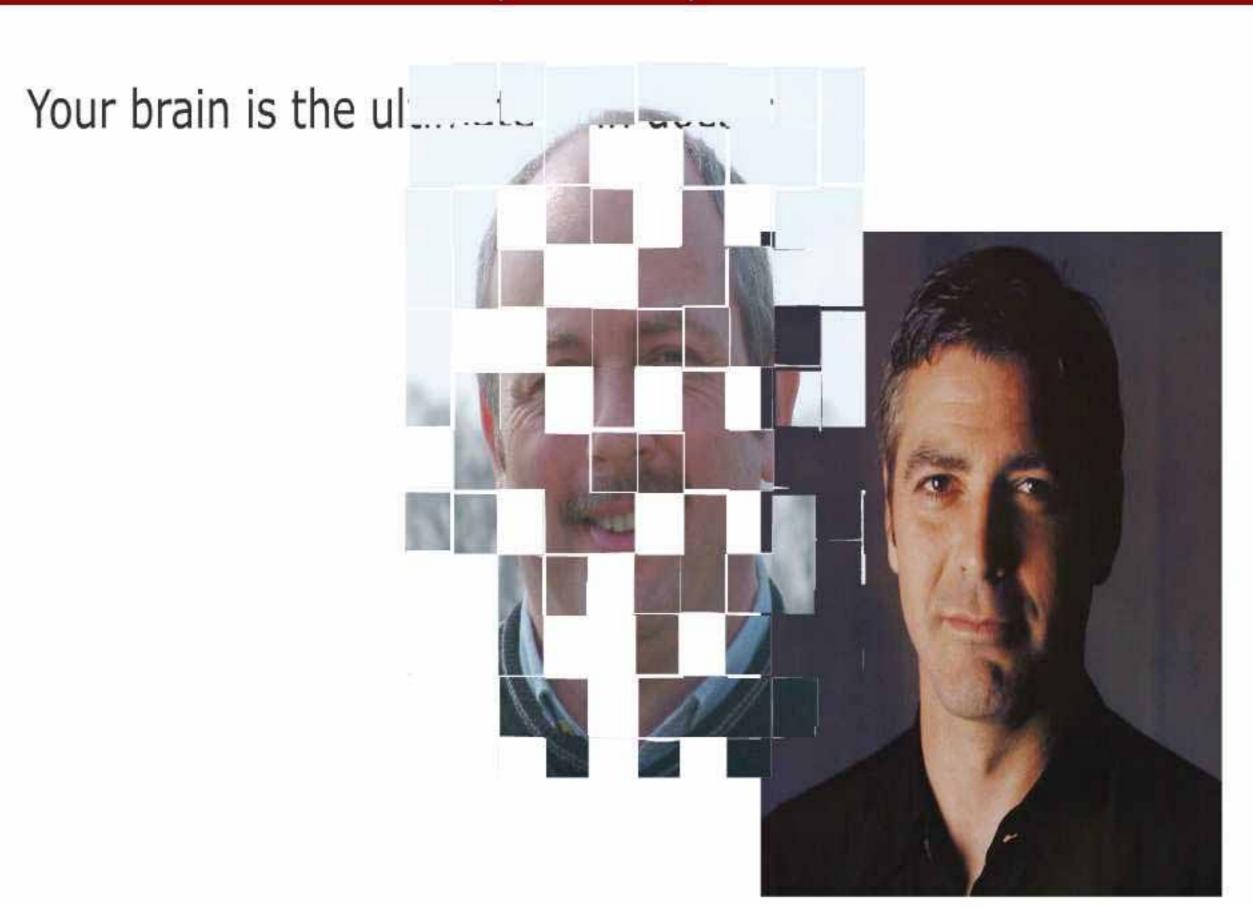


Why does the brain distort memory for events?

Active recall only brings back snippets of information

The brain fills in the blanks in whatever way seems suitable





Your brain is the ultimate spin doctor

The past is seen through rose-tinted glasses

## Some general conclusions

Our rhythms are our own but are harmonised with nature

Our bodies are full of highly accurate molecular-based clocks

Frequent disruption of your body clocks is bad for health

## Some general conclusions

Our rhythms are our own but are harmonised with nature

Our bodies are full of highly accurate molecular-based clocks

Frequent disruption of your body clocks is bad for health

Understanding control of body clocks may help in the fight against cancer

With medical treatments when they are given may be as important as what they are

## Some general conclusions

Birds and bees know more about time than sex

Time passes more quickly when you're having fun

Men and women may not see time passing in the same way

Conscious mental time travel may be unique to humans

Time progressively distorts the brain's version of past events