Biological clocks: Human and animal concepts of time

Transcript

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As humans we live in a world where time can be measured by atomic clocks to accuracies in nanoseconds across millennia. We have external devices of all sorts to help keeps us in touch with the fourth dimension even if we can’t easily experience it. Even without our ingenious time-pieces, calendars and TV and radio programme schedules we can always fall back on mother nature with its regular tidal (12h), solar (day/night -24h), lunar (29.5 days) and terrestrial (365.25 days for the earth’s rotation) cycles.

Question: With all these external zeitgebers (time-givers) to provide us with accurate time information is there any need to have a biological clock?

Answer: All biological organisms from single cells to whole organs from plants to animals, including humans, have, use and depend upon internal biological clocks to function normally.

In short our bodies resemble the classic nightmare shop full of ticking and chiming clocks which only stop when you, or individual cells in your body, die. Rather than being wound up mechanically or powered by batteries our biological clocks are fuelled by the energy we derive from food. As with the clocks in a clock shop the individual accuracies of biological clocks will vary slightly. Just as they rely on the clockmaker adjusting and resetting them to maintain accuracy, so our biological clocks rely on external zeitgebers (particularly light/dark cycles) to do this.

So we don’t just dance to the rhythms of the world around us we dance to our own tunes, albeit with that tune being kept in harmony with the rhythms going on around us. As Michael Althsuler has aptly put it:

“The bad news is time flies. The good news is you’re the pilot.”

We all wonder at the implications of understanding, or even controlling, dimensional and cosmological time. The possibilities of time-travel and revealing the origins and future of the universe are highly engaging subjects for human imagination. However, a similar understanding of what controls biological time and time perception by complex nervous systems is equally fascinating. As we will see, the knowledge we have gained so far already has far reaching consequences for understanding how our bodies function, the way we live our lives and even how we treat major human diseases.

For humans, at least, mental time travel is actually an everyday occurrence. We are highly accomplished time travellers without the need of an HG Wells time-machine. How we accomplish mental time travel; whether other species can do this as well; how our time perception can become distorted by a whole range of different circumstances are still questions that we do not have complete answers for.

This lecture will therefore focus on revealing the nature and location of our biological clocks and then consider how we and other species may perceive, use and even experience time.

A brief history of time in a biological context

It is traditional to put complex areas of science into an historical context to help people to understand the process whereby we have arrived at our current level of understanding in a particular field. In the context of the current topic of biological time then Foster and Kreitzman’s highly accessible book “Rhythms of Life” (2004) deals with this in detail as well as providing a more in depth review of the whole field than can be achieved in a short essay.

The first scientific investigations trying to establish the presence of internal biological clocks seem to have been made by the French astronomer de Mairan in 1729. He observed that Mimosa plants continued to open and close their leaves rhythmically even when deprived of light in a dark cupboard (i.e. they exhibit an intrinsic circadian – 24h – rhythm that was independent of external cues). Carl von Linné in 1751 exploited the accurate (<30 min variation a day) but different rhythms of flower opening in two species of daisy (hawk’s-beard and hawkbit) to construct his famous floral clock (Carolus Linnaeus)
However, it was not until the 1930s that sufficiently rigorous experiments by Erwin Bünning completely established that plants could indeed exhibit a hardwired free-running circadian rhythm that could not be explained by external cues.

After that, examples of these internally regulated biological rhythms have come thick and fast in both plant and animal kingdoms from bacteria through to the most complex organisms on the planet. While all organisms have examples of strong circadian (around a day i.e. 24h) rhythms there are also longer cycles such as ovarian and menstrual cycles (in mammals from 4 days to a month) and circannual (around a year) seasonal rhythms governing activities such as reproduction, birth, migration and hibernation. These cycles are kept in phase by external cues (principally light) from solar and lunar cycles and by the earth rotating on its axis in relation to the sun. The process by which external signals from light, and also other factors such as food, can advance or delay the timing of these internal biological rhythms is called “entrainment”.

However, the duration of these cycles pales into insignificance when we consider the reproductive cycle of the cicada which peaks over a two week period every 13 or 17 years. However, the longevities of animal rhythms are dwarfed by some plants. Bamboo plants for example flower every seven years (spare a thought for the Giant Panda for who this is a favourite tipple!) and some plants even take 100 years to flower (*Agave Americana*). It would seem that the plant rather than the animal kingdom has the best examples of patience!

There is indeed a biological time for everything!

Let's just consider for a moment the extent to which particular human activities, and physiological and biochemical changes in our bodies occur rhythmically during each day.

While our hearts beat rhythmically all the time, resting heart rates are highest between 8 and 10am when we also have peaks in blood pressure and bowel movement. The latter is least active between 10 and 12pm. Our core body temperature is at its lowest between 4 and 6am and at its highest between 6 and 8pm. Concentration, short-term memory and logical reasoning are all at their best between 10am and 2pm – and yet, in the workplace at least, we tend to spend at least a third of this peak cognitive period on tea/coffee breaks and lunch! Perhaps this is no accident however since our ancestors would clearly have needed to be at their sharpest mentally at this time to catch the food to fill their bellies with, rather than simply ordering it from a restaurant or cafeteria or taking it out of a lunch box!

Although we may think that babies can be born at any time, here again there is also a peak between 4 and 6am which is similar to many other diurnal mammals.

From a biochemical viewpoint peak productions usually occur during the hours when we are asleep. As I discussed in my previous lecture (“To sleep perchance to dream” on 26th January 2004) it makes sense for the body to carry out many restorative, growth and metabolic activities when we are asleep since they could interfere with our ability to function if they happened while we were awake. This is also why it would not be a simple matter to evolve towards a more sheep-like pattern of short-duration sleep!

To give a flavour of some of these nocturnal biochemical changes, growth hormone is at its highest between midnight and 2am (during the deepest stages – 3 and 4 - of sleep) and a whole host of substances (prolactin, glucose, melatonin, adrenocorticotropic hormone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone) show peak release between 2 and 6am. Production of lymphocytes and eosinophils also peaks between 2 and 4am. Finally, between 6 and 8am cortisol, testosterone, plasma adrenaline and noradrenaline, blood platelet viscosity, fibrinolytic and natural killer cell activity reach a maximum. Thus blood, immune and endocrine systems are mainly active at night. An exception to this is insulin which peaks between 2 and 4pm in the afternoon although this makes obvious sense in relation to food intake.

It is not just normal bodily functions that peak at particular times of day however; diseases and even death are time-dependent. Gout and cerebral infarction peak between midnight and 2am, gastric ulcer, gall bladder and asthma problems between 2 and 6am, rheumatoid arthritis, hay fever, migraine and angina peak between 6 and 8am. Heart attacks, strokes and death at most likely between 6 and 12am. Osteoarthritis attacks peak between 4 and 6pm in the afternoon and heightened skin sensitivity and menopausal flushes between 8 and 10pm at night.

The “why” in this case is the easiest to part to answer. To start off it is easiest simply to quote the following insight by an unknown author:
“Time is God’s way of keeping everything from happening at once.”

This is precisely what biological clocks are for: making sure that the vast numbers of behavioural, physiological and biochemical changes that occur in living organisms do so in the right sequence and the right time of day, or month or even year to be of maximum benefit. A mundane example of this is that you don’t want to have your sleep disrupted every night by a desperate need to have a pee! This is easily controlled, at least until you reach an advanced age, by your kidneys being less active at night.

The timing of many reproductive events is often closely linked with food supply and external temperature. Species that are seasonal breeders (like many ungulates) need an annual clock to help them regulate when it is best to conceive so that they subsequently give birth and nurture young when climatic and food supply conditions are optimal. Similarly, species that migrate or hibernate need to know precisely what time of the year to do this.

A final important justification for having an internal clock is that if we were totally dependent upon external cues for regulating our rhythmical body functions it would be difficult for any species to have survived sudden climatic changes caused by meteor or comet strikes, volcanic activity etc. More important still, from a routine point of view, is that our biological clocks are organised to prepare us in advance for changes in our external environment that are important for our survival - such as preparing us for waking up in a full state of readiness the moment it gets light. If our bodily changes were only triggered by external cues then we would not be fully ready to take advantage of (or protect ourselves from) them. An important take home message here is that having internal biological clocks allows us to anticipate nature as well as to exist in harmony with it.

The “where” question is more difficult to answer because it seems that the harder we look for them the more examples of clocks we find:

**Cellular clocks**

As far as we can tell most biological cells undergo cyclical changes in growth, metabolism, synthesis, proliferation and even death. This in itself does not mean that they have internal clocks but a considerable amount of research now supports the idea that they all carry the machinery to run internal clocks if required. Not surprisingly many cell cycle changes are circadian in that they too like to run their activities in accordance within a rhythmic framework that is often a 24h-based cycle. They can also entrained in response to food intake via changes in blood glucose.

The most notable example of these cell-based rhythms is cells that undergo the classic mitotic cycle which comprises four stages. When the clock starts in this case the cell moves first into stage G1 (or gap one) where it increases in size and prepares to copy its DNA. Once this preparation is made the cell moves into a synthesis phase (S Phase) when it makes copies of its entire DNA. It then moves into a second gap stage (G2) and then finally divides into two identical cells mitosis or M phase). In this case whether cells will activate their clocks to enter this cycle is determined by chemical signals they receive from each other. In this way cycles are synchronised across multiple cells in a region of body tissue.

**Body clocks**

A number of body organs and tissues outside of the brain have now been shown to have free running internal clocks. Like cells, many of these can to be entrained by glucose changes stimulated by feeding. Examples of tissues with these peripheral clocks are the heart, liver, bowel, kidneys and embryos. Some animal species also seem to have clocks in their retinas to prepare their photoreceptors in advance of day break.

**Brain clocks**

We have known for some time that the main clock in the brain is localised at its base in a general region called the hypothalamus. This is important for the control of motivated behaviours (sex, hunger and thirst) as well as for control of pituitary hormone release governing our reproductive endocrinology and other endocrine organs such as the adrenal and thyroid glands. The clock has now been localised to a small part of this region called the suprachiasmatic nucleus. These nuclei only have some 20,000 neurones and yet their activity influences almost every aspect of bodily function.

If recordings of the electrical activity of neurones in the suprachiasmatic nucleus are made they reveal clear circadian patterns with cells firing more vigorously during the day and less at night. This synchronised pattern continues even if the nucleus is removed from the brain and placed in total isolation in a culture dish. Animal research has shown that if this region is removed
then regular circadian behavioural and endocrine rhythms are disrupted.

The entrainment of this brain clock by light is achieved through direct connections from photoreceptors in the retina via the optic nerve. These projections are separate from those that deal with visual perception via the thalamus and visual cortex. It also appears that special non-rod, non-cone photoreceptors in the retina are used for this photoperiodic signal to the brain. This explains why blind individuals can sometimes show normal photoperiodic responses even though they cannot see because these special photoreceptors may still be functional.

So how does this brain clock communicate time to the rest of the brain? The first clear link to be established was direct neural connections between the suprachiasmatic nucleus and the pineal gland. The pineal gland and the pituitary are the only brain regions that are not bilaterally represented in the brain, even though the structures that regulate their activities are. This makes sense because they perform general hormone secretory roles which do not require any form of hemispheric localisation. However, the uniqueness of the pineal gland as a single brain structure had Descartes elevate its importance by claiming it might be the “seat of the soul”. The reasoning in his case was that you could only have one soul and not two! What the pineal gland does do is less metaphysical however, it secretes the hormone melatonin. This promotes sleep, among other things, and is therefore produced more at night than during the day.

However, generally connections between the suprachiasmatic nucleus and other brain regions are relatively sparse. Experiments have now shown that if this nucleus is removed bilaterally from the brain then foetal donor implants of the same brain region can restore many normal circadian rhythms, even though such grafts do not make extensive connections with the host brain. Indeed, the same therapeutic effects of these grafts can be obtained if they are simply implanted into the brain ventricles where they have no possibility of making appropriate neural connections.

Grafting experiments have also been used to completely establish the fact that the suprachiasmatic nucleus carries the master timing programmes within it and does not rely on other structures. Syrian hamsters can have a spontaneous genetic mutation which inactivates expression of a single gene called “tau”. The animals carrying this mutation show a 22h circadian rhythm in their activity compared with a normal 24.1h one. If grafts from these mutants are implanted into normal animals that no longer have their own suprachiasmatic nuclei they also show 22h activity rhythms rather than 24.1h ones.

What all this means is that the suprachiasmatic nucleus is a self-contained clock which, like the pineal gland, is mainly communicating its temporal signals to the rest of the brain chemically. The problem is that we have not yet identified what all the key chemical signals are. One peptide that is released is arginine vasopressin which can have effects on blood pressure, stress responses, kidney function, paternal behaviour and even aspects of memory function. However, foetal implants of the suprachiasmatic nucleus where this peptide is absent still recover circadian rhythms, so it can’t be that important for this.

The most promising candidate to date is another peptide called prokineticin. The production of this seems to be controlled by the suprachiasmatic clock. Its rhythm can be entrained by light and if it is infused in the brain of a rat during the night, when levels of the peptide are normally low and the rat is very active, then it reduces its activity levels to those seen during the day (Cheng et al, 2002). Thus the peptide would seem to be important for suppressing activity at times of the day when the animals should be sleeping.

It is clear that identification of which molecules, other than melatonin, arginine vasopressin and prokineticin, do communicate temporal information from the suprachiasmatic nucleus to the rest of the brain and body is a major priority for future research since they will offer significant therapeutic opportunities for correcting aberrant behavioural and physiological rhythms.

The brain clock and seasonal rhythms

The reproductive, migratory and hibernation behaviours of many mammals and birds are highly seasonal and extremely well regulated. The brain clock in the suprachiasmatic nucleus is also important for this by responding to feedback from the different durations of melatonin secretion it promotes itself from the pineal gland. Without a suprachiasmatic nucleus squirrels will not hibernate and sheep and hamsters will not show seasonal changes in their sexual activities. For example, the suprachiasmatic nucleus uses feedback information from melatonin secretion duration to control the activity of the gonadotrophin releasing hormone neurones. These are also in the hypothalamus of the female brain and determine whether or not the pituitary will release luteinizing hormone and follicle stimulating hormone to stimulate ovulatory cycles.

Similar control over pituitary release of another hormone, prolactin, is used to promote seasonal changes in food intake, metabolic rate, winter coat length and even colour.
The brain clock as master and commander

While it is easy to conceive of the brain clock as some form of master clock that synchronises all the clocks throughout the body, this is too simplistic a notion since peripheral clocks can run out of phase, and relatively independent of, the one in the brain. However, it is true to say that the brain clock can influence some time-keeping aspects of the running of most, if not all, of the clocks in the body. As we will see in a minute this is particularly well illustrated with control over cell division in the context of cancer.

How do biological clocks work?

It will come as no great surprise to learn that the question of “how” biological clocks work is the most difficult to answer. However, the last 10 years or so has revolutionised our understanding of the inner molecular workings of biological clocks. Whether these clocks are in the brain or peripheral organs or cells there are a number of similarities in the molecular cogs and oscillators involved.

Whether you are talking about a biological or any other kind of clock there is a central requirement for some form of oscillator. For a circadian biological clock the oscillation period is once every 24 hours whereas the clock on a computer for example may be many million oscillations a second (10 megahertz for example would be 10 million oscillations per second). Indeed, if we get down to absolute basics every atom in the physical world is oscillating at around $10^{16}$Hz ($10,000,000,000,000,000$ cycles per second).

In the case of biological clocks the oscillator must be capable of being reset by inputs from external cues (light, temperature, feeding etc) and to communicate its output to the parts of the brain and body carrying out the functions requiring rhythmical control. We also know that within individuals the accuracy of most biological rhythms is $<0.5\%$ (5 minutes a day on a 24h cycle) so biological oscillators must be very accurate. We are used to oscillators in man-made clocks involving pendulums, springs, crystals and even resonating atoms. What would a biological oscillator involving genes and proteins look like? In theory it should be quite possible to use the processes governing gene transcription from DNA through to its translation into proteins which can then act to modulate subsequent gene transcriptions. Biological auto-feedback loops of this kind can effectively be self-perpetuating provided that an energy source is maintained.

The search for the genes and associated proteins that make up these putative molecular clocks has been intense and highly fruitful. We now have working models of a number of central and peripheral clocks in simple organisms, plants, flies and mice. The good news is that they do all work as predicted using feedback loops, the bad news is that there are multiple players and loops and these can vary somewhat between different forms of life (clocks in plants and animals do not have many similar molecular components) and even within different cells/tissues in the same organism.

It is not my purpose here to try to provide full details of these different molecular clocks. These can be found elsewhere (Canaple et al, 2003 - animal cells; Dunlap et al., 2004; Foster and Kreitzman, 2004 - peripheral and central clocks in animals and plants and Yanovsky and Kay, 2003 - plants).

The first clock gene was found in a mutagenesis screen in flies (drosophila) and was called a period gene (per) which produced an associated period protein (PER). Without this gene the animals become arrhythmic. Work with mice, particularly by Takahashi and his colleagues in the USA, showed that there were actually three of these period genes (per1, per2 and per3) and their associated proteins (PER1, PER2 and PER3). In mice we now know that these and other genes (notably cryptochrome genes cry1 and cry2 and genes such as rev-erb α and ROR α,β and γ) act to control two key transcriptional activators called CLOCK and BMAL1 which act together as a heterodimer to control the expression of the period and other clock genes. CLOCK and BMAL1 also act to control the expression of genes responsible for translating the information from this clock to other areas controlling behavioural, physiological and endocrine functions (these are simply identified at this stage as clock-controlled genes - ccgs – so far the only two to be identified are arginine vasopressin and prokineticin).

Looking at the final 24h output of this mouse molecular clock in terms of CLOCK/BMAL1 activity and that of PER, CRY, REV-ERB and ROR there is about a 6h phase shift in their peaks and troughs because of the time it takes for their respective positive (CLOCK/BMAL1 increases PER, CRY, REV-ERB and CCGs) and negative (PER/CRY as a dimer and REV-ERB decrease CLOCK/BMAL1) feedback effects on each other.

The result is that we have a 24h oscillation sequence where, at time zero, CLOCK/BMAL1 levels are rising and those of PER, CRY, REV-ERB and CCGs are low; at 6h into the cycle CLOCK/BMAL1 levels reach their peak and have now stimulated those of
PER, CRY, REV-ERB and CCGs to rise; by 12h CLOCK/BMAL1 levels have started to fall because they are now being inhibited by PER, CRY and REV-ERB levels which are at their peak; by 18h CLOCK/BMAL1 levels have reached their lowest point although PER/CRY, REV-ERB and CCGs are also falling because they are now not being stimulated by CLOCK/BMAL1 any more and are degrading; by 24h we are back to the same pattern as at time 0 where CLOCK/BMAL1 levels are starting to rise because they are no longer inhibited by PER/CRY and REV-ERB which are at minimum levels. Here we have the makings of a highly accurate 24h molecular clock!

Light itself can influence this system by directly influencing per1 and per2 gene expression. This leads to production of PER1 and PER2. If this happens in the evening (time 0 above) when levels of PER and CRY are low then it seems that PER2 can either directly or indirectly increase bmal1 gene expression and prolong BMAL1/CLOCK protein production thereby delaying the whole cycle. On the other hand if exposure to light occurs after the middle of the night (between 6 and 12h) when BMAL1/CLOCK protein levels are falling and both PER and CRY levels are high, then increased PER1 and PER2 levels may cause more PER/CRY dimers to form and these act to reduce BMAL/CLOCK levels quicker than usual and this ends up advancing the cycle.

The fun part is that this sequence of events is likely to be much too simplistic and fine tuning of the system is probably under the control of many more genes and proteins and it will take a chess master or a computer to be able to calculate the impact of all the potential interactions!

**Consequences of clock malfunctions and ways to reduce them.**

The consequences of biological clocks having problems telling the time are not simply being late for an important meeting, nor are they as easily fixed by getting them repaired by a medical watchmaker or changing a battery. When biological clocks malfunction the result can make life miserable and may even lead to disease and death.

**Jet lag – the problem**

The millions of years of evolution that have shaped our biological clocks, and those of other species, clearly could not have taken into account our modern needs to get to different parts of our planet far faster than our clocks are designed to cope with altered time zones. On average it takes our biological clocks one whole day to adjust for each 1 hour time zone crossed, so they we need around 5 days to adjust to a transatlantic flight from London to New York or Washington (5h time difference).

Jet lag symptoms illustrate how central and peripheral clocks have some degree of independent control. After a long-haul flight, jet-jag symptoms are often tolerable initially but become worse after two to three days. The first effects of the time change are to throw all the biological clocks out of phase but the effects get worse because the central clocks re-adjust quicker than the peripheral ones and by two to three days the two sets of clocks are pulling against each other. This latter situation is actually worse than having all our clocks at sixes and sevens. In future it will be important to find ways of improving the control that the brain clock has over these rather less adaptable peripheral ones if we want to find a more effective way of treating jet-lag symptoms.

**Jet-lag – possible ways of alleviating problems**

If one is involved in a short-duration round trip, and the time difference is not too great, then jet-lag can be reduced or avoided by not changing your watch and staying on your own time. However, this can mean having to shut yourself in a darkened hotel room in the late afternoon when it is still light outside and everyone else is awake, or alternatively walking around wondering what to do when everyone else is asleep.

Foster and Kreitzman (2004) suggest ways of speeding up adaptation to time zone changes by controlled exposure to light at different times of day. The effect of light exposure can be to either advance or delay your biological clocks dependent upon you core body temperature. Light exposure after body temperature minimum (around 4 am ) will delay your clocks whereas before this it will advance them.

So if you are travelling west, and need to delay the onset of sleep then when you arrive at your destination, you should expose your eyes to late afternoon/evening light for several days when crossing 2-8 time zones. If you are crossing 8-12 time zones then expose your eyes to early morning light.

If you are travelling east you need to advance the onset of sleep and so avoid exposing your eyes to early morning light but do expose them to late morning and early afternoon light when crossing 2-8 time zones. If crossing 8-12 time zones morning light
must be avoided and your eyes exposed to mid-afternoon or evening light. Avoiding exposure to morning light in these cases can be achieved using dark glasses.

Taking melatonin

The natural sleep-promoting hormone produced by the pineal gland can be purchased in 5mg doses in the USA where it is licensed for use (but not in the UK). It can be effective in reducing jet-lag symptoms but only if taken at the right time and not for time differences of less than 5h. Advice paraphrased from Foster and Kreitzman (2004) is:

If travelling West you need to delay sleep onset and a capsule needs to be taken first at local bedtime (11.00pm or later) and for 4-days after arrival. If you wake up before 4am another capsule can be taken but not after this since it can make you sleepy in the morning. In this case melatonin should not be taken before the outward flight.

If travelling East you need to advance the onset of sleep and the first capsule should be ideally taken prior to or during the outward flight at whatever time is equivalent to bedtime at your final destination. After this further capsules should be taken for 4-days at local bedtime.

Warning: “Melatonin can induce sleepiness and lowered alertness in sensitive individuals. You are advised not to drive, operate heavy or dangerous machinery, or do equivalent tasks requiring alertness, for four or five hours after taking melatonin. Long-haul pilots and crew are advised not to use melatonin, because of the potential difficulties with timing the dose. If you, or a close blood relative, suffer from a psychiatric condition or migraine you are advised not to use melatonin. If you are under 18 years old or know (or suspect) that you are pregnant you are advised not to use melatonin. Possible side effects are sleepiness, headache (infrequent) and nausea (very infrequent)” from Foster and Kreitzman (2004) page 254.

Shift work

Our 24/7 society requires that many industries and services continue around the clock. Even where there is no public requirement for 24h production there is also greater productivity and profitability to be had from operations that continue around the clock. While our biological clocks can adjust reasonably well to a complete shift in our day and night cycles (so that we can be active at night and sleep during the day) within a few weeks, no one wants to remain on permanent night shift. Chopping and changing shift times is a nightmare for our biological clocks and often leads to states of chronic sleep deprivation where we function mentally and physically well below par.

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. After four successive night shifts a worker has a 50% or higher risk of a crash when driving home in the early morning.

Strategies for coping with shift work

There does not currently seem to be an agreed best policy on this. Even if one works permanent night shifts there is a risk that sleep quality will be impaired by disturbances during the day when everyone else is active. It is also generally thought that having evolved a diurnal life-style over millions of years we cannot completely adapt to a nocturnal existence. There does appear to be agreement that it is best to do shift work in patterns of at least 1 week on and 1 week off but other factors such as the speed of the shift between one pattern and another and the length of each shift can also have a bearing on how well an individual can cope with working this way. What individuals do at weekends when they are on night shifts may also influence how well they adapt. There is a hypothesis that we are better at adapting to forward progressing shift cycles (days – evenings – nights rather than nights – evenings – days) but this is not fully substantiated.

Seasonal affective disorder (SAD)

Like many other mammals the human circadian pacemaker is able to detect seasonal changes in day length and this can have a number of effects in changing our behaviours and emotions as well as our physiology and biochemistry. For most of us these changes do not cause significant problems. However, for about 3% of people in the UK, and proportionately many more than this in more Northern latitudes where day length during the winter months may only last a few hours, the shortening of the days causes a profound depression. This condition is now referred to as “Seasonal affective disorder” which makes the appropriate acronym of SAD.

Individuals with SAD can be seriously depressed, socially withdrawn, lethargic and even suicidal. They tend to crave
carbohydrates and may put on 5-15 kilograms in weight over the period of short day lengths. With the lengthening of days during spring these symptoms largely disappear.

These SAD symptoms resemble those exhibited by hibernating animal species, particularly the lethargy and weight gain. It is possible that in humans this is a vestigial trait from our ancestors living in the most northern latitudes where winter was a time for inactivity and reserving energy stores. Equally, feelings of depression caused by the shortening days may have promoted migration towards more Southern latitudes.

Treatments for SAD

Typically this condition is treated by exposing individuals to high intensity light sources that resemble normal day light. They are exposed to banks of lights delivering around 2500 lux (similar to light levels on a cloudy day) for around 45 minutes at a critical period of the day when it seems to be most effective (between 3.30 and 8 am). From this observation it seems clear that exposure to early morning light is the critical element in keeping us in a positive mood. Unfortunately, just turning the bedroom light on during dark winter mornings is not enough since normal artificial lighting will only produce a few hundred lux (which is somewhat pathetic compared to daylight levels on a sunny day which may go as high as 100,000 lux!).

Old age

As I discussed briefly in my last talk on sleep, one of the unfortunate effects of getting older is that our patterns of sleep are affected. Typically, sleep duration is reduced by around three-quarters of an hour (compared with the standard 8h when we are younger), we spend a reduced amount of time in the deep stages of sleep (stages 3 and 4 thereby losing our growth hormone peak) and are much more sensitive to external noises. It seems that the main reason for this is that our biological clocks become more erratic as we age and this not only influences sleep but many of our other behavioural and physiological functions as well.

In general, the main effect of age is to reduce the amplitude of many rhythms (for example body temperature, oxygen consumption, hormone production - i.e. melatonin, growth hormone, testosterone, luteinizing hormone: insulin production in humans actually increases). Another significant effect of getting older is that there is an uncoupling (desynchronising) of your various biological rhythms (the body clocks are more at sixes and sevens with one another rather like the initial effects of jet lag).

Potential therapies for old clocks

The simple answer to this is that there is no miracle advice as yet. It will certainly help if we try to live lives that keep our clocks stable while we are young and continue to maintain this regularity when we are old. This can be difficult to achieve however.

Much has been claimed for the benefits of taking melatonin to keep everything regular; however no serious study has yet established that this is an effective or even safe long-term approach, even if it is a natural hormone. It is also possible that in time we might be able to take cocktails of clock-controlled proteins to help control and synchronise all of our rhythms.

At the extreme end of the spectrum there might be a suprachiasmatic nucleus transplant to consider, although in this case the benefits would probably not outweigh the risks!

Cancer

The relationship between clock genes and cancer is now well established. I have already shown how dividing cells have their own clocks and we are all aware that cancer is effectively a problem of cell division that has got out of control. Pretty much every aspect of the cell cycle from growth, synthesis and DNA replication through to final division and ultimately death are under the influence of many of the same clock genes operating in the suprachiasmatic nucleus. For this reason transgenic mice that no longer express the PER2 gene not only are arrhythmic, they are also more susceptible to growing tumours. Similarly animals without a suprachiasmatic nucleus also have accelerated growth of existing tumours (illustrating how the brain clock can influence rhythms in cells in all parts of the body). Cancer cells also have rhythms although they tend to be out of phase with those exhibited by normal cells.

It appears that normally functioning biological clocks in the body, and particularly the brain, are able to act as tumour suppressors by careful regulation of the molecules that control cell proliferation, damage and death. A frightening, but logical
extension of this conclusion is that if we deliberately mess up the normal functions of our clocks by extensive long-distance travel, shift work and irregular sleep patterns we might increase our risk of developing cancers. Unfortunately this conclusion seems to be correct. We also seem to increase the risk of cardiovascular diseases.

On the plus side perhaps future therapeutic approaches targeting clock genes may prove to be effective in helping us fight this disease.

**It's time for your medicine dear!**

Our increasing understanding of the importance of biological rhythms and clocks has led to a whole new approach in Western medicine “chronotherapy”. I say Western because many Eastern cultures, notably Chinese medicine, have practiced for years the idea of tailoring medicines to the rhythms of each individual. Given the huge changes that we have in our organ function, biochemistry and metabolism each day and in relation to menstrual cycles it is perhaps a little surprising that scant attention has been paid to the idea that when you give a medicine may be almost as important as what it is.

A good example of this is chemotherapy for cancer treatment. I have already mentioned that cancer cells cycle out of phase with normal cells and a key problem with chemotherapy is killing the cancer cells without harming the normal ones. Cells are more vulnerable to damage at some stages of their cycles than others (notably the synthesis phase). In principle one could time chemotherapy treatment for when cancer cells are at this vulnerable stage whereas normal cells are not. An advantage of doing this should also be that a higher, more effective dose of chemotherapy could be given because the normal cells would be at a less vulnerable stage of their cycle. It would seem that this may well be the case. Dr Francis Lévi in Paris has reported that in colon cancer patients by timing administration of chemotherapy drugs in this way up to a 40% higher dose could be tolerated and there was a 3-fold increase in the number of tumours that shrunk by 50% or more (Lévi et al, 2001).

This ability of drug timing to aid the effectiveness of cancer treatment was also shown back in 1985 by Hrushesky in a group of women with ovarian cancer (Hrushesky, 1985).

A number of other cancers show seasonal patterns (notably cervical, breast and testicular) and this information could be used to time screening programmes optimally as well as design treatment regimes.

Foster and Kreitzman (2004) in their book also give examples of treatment of other diseases with circadian rhythms such as rheumatoid arthritis (which peaks around 6-8am ) and osteoarthritis (which peaks around 4-6pm ).

**Time and the birds and the bees!**

Sex and all aspects of reproduction are of course highly rhythmic and these rhythms are of fundamental importance to successful breeding in all species. While the birds and the bees have somehow become synonymous with procreation they are far more remarkable in terms of their ability to use and even communicate temporal information.

Bees in particular have been the subjects of intense study. August Forel back in 1910 was the first to consider that bees had some form of memory for time. He observed that they would learn to come back to the same place at the same time each day where they had found jam and sugar irrespective of whether it was actually there. However, it was the pioneering work of von Frisch in the 1950s that really nailed the idea that bees must be able to use temporal information although it was not until the 1990s that the full story has been resolved. Bees are able to communicate to each other the location of distant sources of nectar by means of their “waggle” dance when they re-enter the hive. Components of this figure of eight dance signal the quality, distance and direction of the nectar source. To communicate distance they need to compute their flying time and for direction where the nectar source is in relation to the sun.

However, life being what it is, there is often a considerable delay between finding a pot of gold and being able to tell anyone about it. If a bee returns with the good news too close to curfew then it has to hang up its dancing shoes until morning. By that time the position of the sun will be very different from when the pot of gold was found. Nevertheless the bee is still able to communicate the correct direction co-ordinates in relation to the current position of the sun (the sun would move about 15 o an hour in relation to the hive). Just to make things even more remarkable they can do all this on a cloudy day by detecting patterns of polarisation of the light. In short these small, simple animals have an amazing global positioning capability which is afforded to them by being able to use the sun to calculate different times of day. Bees can even learn to associate particular flower scents with specific times of day!
Birds are also champion time users. When migrating birds fly South they may use the stars and even magnetic fields to guide them but they also need temporal cues. They have to calculate when to fly South, how far they should go and when they should return. Getting this wrong may mean you don’t join up with all your mates and get the best spot on the beach (or more importantly the best nest sites). To do this it appears they actually have two different clocks, a circannual clock that strikes once a year and the more standard 24h circadian clock.

Birds and bees may perhaps be the superstars of time users but it is clear that all animals have some capacity to use time whether in terms of exhibiting the correct temporal sequencing of complex behaviours or being able to turn up at the same place at the same time each day. Laboratory animals such as rats can eventually be trained to use temporal cues to predict availability of reinforcers such as food.

There are also of course more impressive claims from the animal world particularly involving pets such as cats and dogs. Rupert Sheldrake has devoted a whole book (Sheldrake, 1999) to observations and even experiments designed to show that dogs and cats know exactly when their owners are coming home. While the claim here is that they can somehow pick up on the owner’s intention to return home (even from 1000s of miles away!) the observations on behavioural patterns are highly suggestive of the animals also having the ability to use time to guide their behaviours. Indeed, anyone who has worked with animals will claim that they “know” exactly what time of day different key activities normally take place.

**Time perception and consciousness**

For us time is at the centre of everything we do and see happening around us:

“...And indeed there will be time
For the yellow smoke that slides along the street
Rubbing its back upon the window panes;
There will be time, there will be time
To prepare a face to meet the faces that you meet;
There will be time to murder and create,
And time for all the works and days of hands
That lift and drop a question in your plate;
Time for you and time for me,
And time yet for a hundred indecisions,
And for a hundred visions and revisions,
Before the taking of toast and tea.”

T.S. Eliot – The Love Song of J. Alfred Prufrock

Being able to use time to control and guide behaviour does not immediately equate to either having a conscious perception or a concept of it. The way we humans conceive of time is, rather like our dreams, highly egocentric in that we usually put, present, past or possible future events in the context of our own personal experience. This immediately implies a requirement for self-consciousness to conceive of time in this way. In my lecture on Self-awareness (Knowing you, knowing me”: can other animals have an identity crisis? – March 2003) I concluded that the capacity for self-consciousness was limited even in great apes such as gorillas, chimpanzees and Bonobos. It seems likely therefore that most other species cannot have a similar concept of time as us.

**Mental time travel**

The idea of time travel may hold great fascination for us but we are actually very accomplished time travellers even though, as I
will discuss in a minute, we do not always maintain accurate records of what has happened in the past. It has been argued strongly that mental time travel is unique to humans (see Suddendorf and Busby, 2003). This re-iterates what I have just said about the human concept of time requiring self-consciousness. Indeed, the developmental time course for self-awareness and for the ability to mental time travel is very similar, 2-4 years.

A central requirement for demonstrating the ability to time-travel mentally into the past is that you are able to experience what, when and where something happened in an integrated way. Since many species can achieve this over very short time intervals of seconds or even minutes the criterion used is that they must be able to do this for events that have occurred days, weeks or even years before. This is technically called the ability to display episodic memory (memory for specific events and when and where they happened) and it has been very hard to demonstrate convincingly in any animal species. Indeed, in previous lectures I have espoused a view, supported by a number of scientists, that many animal species live primarily in the present and rely almost entirely on external events in the present for triggering recall of specific memories. In such a context remembering when something happened does not have much significance only what and perhaps where.

Of course if animals could communicate with us using language it would not be a problem to assess whether they can perform mental time travel. However, a series of ingenious experiments by Nicky Clayton (currently at the University of Cambridge) and her colleagues have provided other ways of obtaining this information and mounted a serious challenge to the idea that animals can’t remember when events happened (see Clayton, Bussey and Dickinson, 2003).

She has studied the food caching behaviours of the Western Scrub Jay for a number of years and has revealed their remarkable ability to use time to determine what kind of buried food to dig up and eat. If given the choice of two foods, wax worms or peanuts they like both but much prefer the worms. However, as with all life’s pleasures, the best tend to always last for the least amount of time; worms have a sell by date of only 3 days after which time they are inedible (even perhaps for “I’m a Celebrity get me out of here” contestants!). Once the birds learn this fact, if they bury both peanuts and worms in different sand-filled compartments in a tray they will dig up the worms first if they are given back the tray 4h later. If, on the other hand, they get the tray back after 4 days they only dig up the peanuts. They are not using cues from the food itself because they show the same choice patterns in terms of which compartments they dig in even if the worms and peanuts have been removed!

The Scrub Jays may also be able to see into the future. Once they have experience that other animals may steal the food they have hidden, if they hide it when they know they have been observed, when they subsequently get a chance of a private viewing of their buried hoard they dig up the goodies and bury them in another compartment. If they do not have this experience that other birds can be thieves then they don’t take these precautions. Their behaviour suggests that they are taking precautionary actions to reduce the chances that predicted future events may rob them of their favourite tipple!

While this seems to be impressive evidence that Scrub jays have human-like abilities for mental time travel others dispute this. While most agree that the animals have a form of episodic memory that can link the what-where-when aspects of events some consider that this does not imply that the animals actually mentally travel back to the time when they cached the food. Instead, the “when” component may simply be tagged on to the “what” and “where” bit in some way. The animal would then know what to do when re-presented with the buried food tray without having to consciously think back to the moment in time when it actually buried the food. The only obvious ways to resolve this issue of whether other animals can really mental time travel is to seek answers from language trained apes, or perhaps to use other forms of tasks developed in monkeys where they are able to indicate by choice how confident they are that they can remember something.

**Time perception and the brain**

While the suprachiasmatic nucleus may be extremely important for regulating activity, physiological and biochemical rhythms, time perception seems to depend on other brain systems. In general, timing involving sub-second intervals involves the motor cortex, cerebellum and basal ganglia reflecting the importance of this high speed dimension for the control of motor coordination. Timing involving durations of many seconds or longer tend to involve the frontal and parietal cortex reflecting a greater consciousness component.

The ability to travel mentally back or forward in time to predict likely events in the future has a separate representation in the human brain from other kinds of memory and even self-awareness, although like self-awareness it may involve regions of the frontal cortex. Several humans (such as an individual known simply as KC) who have unfortunately had damage to their brain have been shown to have limited capacity to carry out any form of mental time travel to recall past events or predict future ones.
other than for very short periods (literally a few minutes). These individuals report that when they attempt to travel more distantly into the past or future their minds go completely blank.

**Distortions in time perception**

While for the time pieces we have created, or even biological clocks, one second or minute is virtually identical in duration to every other second or minute, the way our brains interpret and experience time is subject to a huge variety of distortions. Just as our senses can only indirectly interpret what is going on around us due to both the detection limitations of the receptors in our sense organs and the organisation of the brain, so it is with the brain and time. Our subjective psychological experiences of the same unit of actual time can vary considerably. This problem of the relativity of subjective time perception is illustrated admirably by Einstein himself:

“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)

We all know that time flies when you’re having fun and drags when you are not. This is fully substantiated by experiments on time-estimations by humans in different emotional states – when you are happy you underestimate the passage of time and when you are sad you overestimate it. Psychological disorders such as schizophrenia and depression also distort time perception. Even changes in body temperature can alter time perception with high temperature making everything seem longer and low temperature shorter.

There are even reported sex differences in time perception. Women overestimate time periods of less than a minute and underestimate longer periods. Men, as usual, do the opposite. There is a somewhat controversial debate as to why this should be, but the observation might explain why women have a reputation for always being late for assignations (underestimating how much time has passed). As Marilyn Monroe reportedly said:

“I have been on a calendar but never on time!”

It may also represent a functional adaptation to having sex with males who only perform for less than a minute (overestimating how much time has passed). On the other hand this might explain why men think they can do in a minute what women can only do in an hour and why women always seem to be later than they really are.

Perhaps a final salutatory, if somewhat risqué, conclusion from this is that if women think that men take too little time over sex, men know that they take even less time than women think!

Getting back to the more serious aspects of time perception however, if our psychological perception of time is so relative then this immediately raises issues about whether the different senses, nervous systems and life expectancies of other species may make their perception of time different to that of our own.

“So why, Love, should we ever pray
To live a century?
The butterfly that lives a day
Has lived eternity”

And

“If space and time, as sages say,
Are things that cannot be,
The fly that lives a single day
Has lived as long as we.
T.S. Eliot (from a Lyric and Song)
Drugs and time perception

One of the potential pleasurable feel-good experiences of some mind expanding drugs such as cannabis, opium and LSD is the fact that they slow down our perception of time. A minute can indeed seem like an hour. Even in rats cannabis has been shown to prevent them from discriminating short from long intervals.

Withdrawal of addictive drugs such as nicotine (giving up smoking) also results in individuals overestimating time and this may contribute to psychological difficulties in breaking drug-taking habits.

Time effects on the accuracy of memory

We may all think that our brains are accurate storers of important events but this is not true. A recent study in the USA tested the abilities of individuals to recall events reported in the O.J. Simpson trial. Whereas after 15 months 50% were highly accurate in recalling the facts and only 11% of individuals introduced major distortions by 32 months only 29% were accurate and 40% had major distortions of fact (Schmolck, Buffalo and Squire, 2000).

It seems that we should not rely on our brains as long-term accurate repositories of events. Given how long legal proceedings can last this creates potential alarm bells for a witness based judicial system. Perhaps keeping diaries is after all a much more reliable way of recording your past than relying on your brain.

The probable reason why time distorts the way you remember events is that each time you remember them your brain tends to reconstruct the memory with snippets of actual information and then fills in the blanks using other aspects of generic experience. In this way events in the past can become progressively distorted by this filling in process so that events more resemble how your own experience thinks they should be than the way they actually occurred. No wonder our memories of the past often seem to be viewed through rose-tinted glasses!

Do changes in our brains really make our perception of time go faster as we get older? For the time being I will leave this question to my next lecture (Turning back the hands of time: growing old gracefully – 25th March 2004).

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

Birds and bees know more about time than sex

Time passes more quickly when you’re having fun

Conscious mental time travel may be unique to humans

Time progressively distorts the brain’s version of past events

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Selected references:


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