already extensive evidence from fMRI and architectonic studies that the human brain contains many more cortical areas (possibly 150 or more) than the brains of macaque monkeys. One would also expect areas to be more frequently subdivided into sets of modules or columns of functionally related neurons, such as the three types of bands of neurons subdividing the second visual area, V2, of primates, but there is only limited evidence for this. However, the premise that hemispheric asymmetries increase with brain size in order to reduce the need for costly interhemispheric communication is well supported by the extensive evidence for hemispheric specializations in the human brain related to handedness, language, attention, memory and object recognition.

In conclusion, an outline of the course of the evolution of the human brain is starting to emerge. Great progress in the gathering of relevant data has occurred over the last 20–30 years. A more complete description could easily occupy a series of volumes, and interested readers are invited to read further. Most importantly, there is much yet to be gained by applying current methods of investigation so that future reviews can be better informed and greatly enriched.

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Chronic jet-lag increases mortality in aged mice

A.J. Davidson, M.T. Sellix, J. Daniel, S. Yamazaki, M. Menaker and G.D. Block

Despite the fact that trans-meridian travel and shift work are commonplace in our 24/7 society, few controlled studies have addressed the health effects of repeated phase shifts of the biological clock. Shift work [1] and chronic jet-lag [2] reduce mental acuity and increase the risk of a number of medical problems, including cancer, peptic ulcers and sleep disorders. Some of these problems become more severe with the number of years on the job, the result either of cumulative damage or the increased age of the subjects [3]. In general, morbidity associated with many organic disorders is increased in the aged; however, the role played by age-associated alterations in the circadian clock is poorly understood. In particular the effect of repeated schedule changes is largely unaddressed. Here we report evidence that chronic jeg-lag increases mortality rates in aged mice.

We were led to the current experiment by an observation in an unrelated study where we found that three of eight aged transgenic rats exposed to a 6 hour advance of the light cycle died following the light schedule change. In contrast, no deaths were observed if the light cycle was delayed. In order to explore whether the effects of light schedule changes on longevity were reproducible in a larger study and observable in another rodent species, we placed young (8–12 month old) and aged (27–31 month old) C57BL/6 male mice on one of three lighting regimens for eight weeks. Nine young and 30 aged mice were maintained on a normal 12:12 light–dark cycle. A second group of young ($n=9$) and old ($n=30$) mice was exposed to a 6 hour advance of the light-cycle once every seven days. The third group of young ($n=9$) and old ($n=28$) mice was phase-delayed by 6 hours once every 7 days. The rotating light schedules were chosen to effect large phase adjustments of the circadian system each week, such as would be expected to occur during flight across time zones or in some situations during rotating shift work cycles.

While younger mice fared well on this 8 week schedule (only one death occurred), we found that aged mice were significantly affected by light schedule changes (Figure 1A,B). At the end of the 8 week period of light schedule rotations there was 47% survival in animals whose light cycle was advanced each week, 68% in those experiencing delays of the light cycle and 83% in unshifted aged mice (chi square, all groups, $p<0.05$ on Day 54). Importantly, chronic stress was not implicated in this phenomenon as total daily fecal corticosterone levels did not increase in aged mice undergoing phase advances or phase delays (see Figure S1 in the Supplemental data published with this article online).

To determine whether the effects of phase advances on mortality might be related to the duration between schedule changes, mice were shifted more rapidly, every 4 days. On this schedule, we found that advancers died more quickly than with weekly shifts (Figure 1C; 60% survival on Day 24). Delayers fared much better than advancers (chi square $p<0.05$ on Day 32). The data suggest that the asymmetry in mortality rates between animals exposed to light schedule advances and delays persists and is possibly enhanced with the shorter inter-shift interval of 4 days.

Our data show that phase-advancing the light cycle hastens the death of aged mice. The mechanism underlying the

deleterious effects of phase advances of the light cycle is unclear. It appears that the mechanism is not stress-related. Other possibilities include sleep deprivation and disruption of the immune system. There is significant complexity in the resetting behavior of the mammalian timing system to phase advances in the light schedule [4] that might play a role in the increased mortality that we observed.

In future experiments it will be important to explore how the length of the interval between shifts affects longevity and whether there is reduced longevity in animals that experience light cycle changes when younger.

Non-standard lighting cycles have repeatedly been shown to hasten death in animals. Fruit flies [5] and blowflies [6] have shorter lifespans when housed in L:D cycles with a period shorter than 21 hours or longer than 27 hours. Cardiomyopathic hamsters exhibited a median life expectancy that was 11.3% shorter if they were housed on a light schedule that was inverted once per week compared with a stationary 14:10 L:D cycle [7].

However, the same shifting schedule did not affect lifespan in CD2F1 mice [8]. A 6 hour phase-shift in the light cycle every two days increased the growth rate of Glasgow osteosarcoma in mice [9]. We believe that ours is the first study providing evidence that differential mortality based on the direction of the shift in the light schedule.

Endogenous circadian oscillations have been detected in nearly all mammalian tissues. Our results lead us to speculate that the internal desynchrony among these functional oscillations that accompanies readjustment to an advanced light schedule may have serious health consequences that are exacerbated in the aged.

There is evidence that the circadian system of aged animals is altered in significant ways [10]. These age-related circadian changes may have an adverse effect on health during phase advances. Alternatively, the general frailty of older animals rather than age-related changes in the circadian system may make them less able to tolerate changes in the light schedule. Whatever the precise mechanism, the dramatic differences in morbidity associated with phase advances of the biological clock

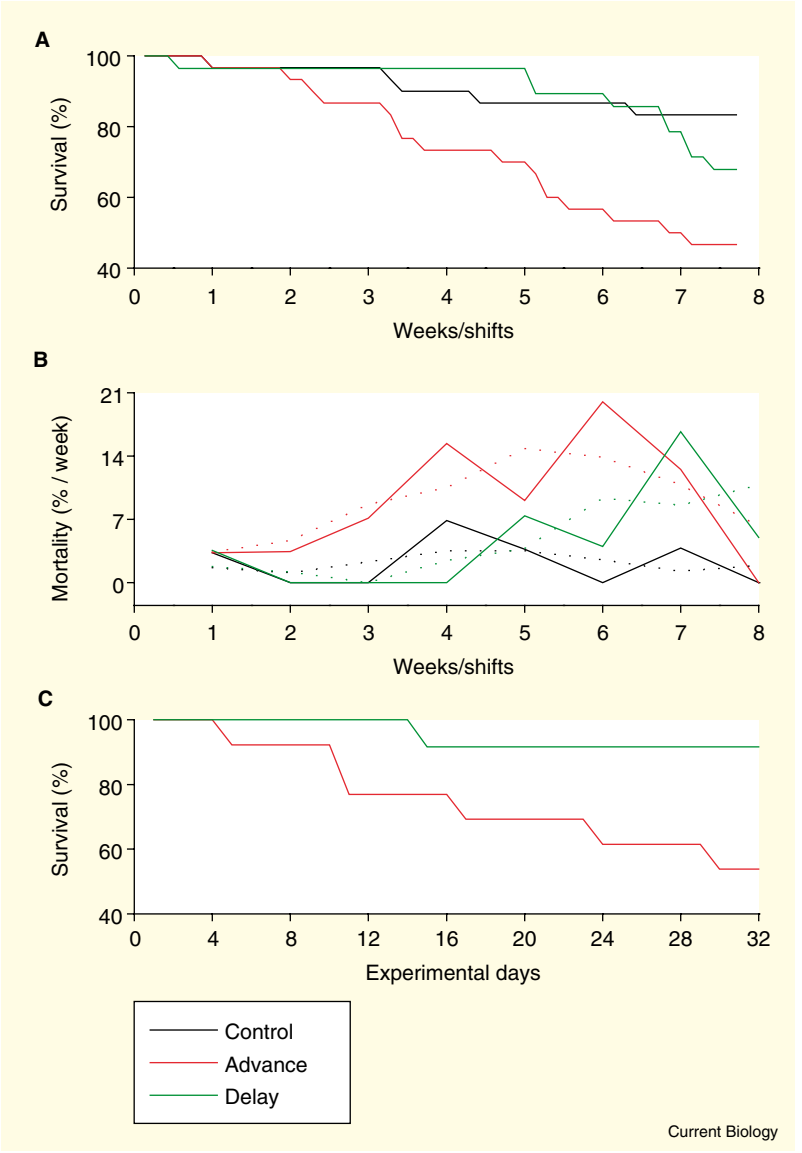

Figure 1. Survival of aged mice undergoing weekly phase shifts of the light cycle.

(A) Survival curves of aged mice undergoing a weekly 6 hour advance or delay adjustment of the light cycle, compared with unshifted aged controls. On Day 56 survival was 47% in advancers, 68% in delayers, and 83% in unshifted aged mice (group sizes are $n=30$ for controls and advancers and $n=28$ for delayers). The distribution of surviving mice at the end of Week 4 ($p<0.05$), Week 5 ($p<0.025$), Week 6 ($p<0.01$), Week 7 ($p<0.01$) and Week 8 ($p<0.05$) of the protocol is significantly different than chance (chi square). Advancers died faster than controls (pairwise Chi square; $p<0.01$, Day 54) but were only different from delayers at the ends of Weeks 6 ($p<0.01$) and 7 ($p<0.025$). (B) Death rate per week of the protocol. % mortality of remaining mice is plotted for each week in bold. Trend-lines (three-point moving average) for each dataset are shown with dotted lines of the same color. Advancers began dying sooner (all 3 groups chi-square; Weeks 3–4, $p<0.025$; Weeks 5–6 $p<0.05$) and the death rate remained higher than the other groups until the final week of the protocol. The death rate in unshifted animals was flat for the duration of the experiment. (C) Survival curves for mice shifted every 4 days. We found that advancers still died at a faster rate ($p<0.05$ on Day 32; group sizes: 13 advancers, 12 delayers).

raise important issues about the safety of counter-clockwise rotating shift work and the potential long-term health consequences for airline crews regularly crossing time zones.

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Supplemental data
Supplemental data including experimental procedures are available at http://www.current-biology.com/cgi/content/full/16/21/R914/DC1

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The importance of procedural knowledge in desert-ant navigation

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Path integration enables a foraging animal to keep a continuously updated estimate of its direction and distance from some reference point — the nest or a frequently visited feeding site — and hence provide it with a global vector pointing from the animal's current position to this reference point [1–5]. This global vector is retrieved and used when the animal later returns to the starting point. Even though path integration is the dominant mechanism in desert-ant navigation, the animals have been shown to use landmark-based routes as well. When following learned sequences of landmarks, the ants are guided by directional information gained from one landmark to the visual catchment area of the next landmark [6–9]. Here we report evidence that the procedural knowledge involved in route learning can dominate the path integrator to such an extent that the ants can even select the opposite direction to that represented by their path-integration global vector.

We trained desert ants, *Cataglyphis fortis*, within a two-leg, U-turn channel array and thus forced them to accomplish a 180° turn when running back and forth between nesting and feeding sites. Subsequently the ants, after they arrived at the feeder, were displaced into a linear test channel in which their homebound courses were recorded (for a detailed description of the methods see the Supplemental data available online).

In the first experiment, the ants were trained within linear channels first to run from the feeder for 6 m to the north, then to turn by 180°, and then to run for another 3 m to the south until they reached the nest (6U3 training paradigm; Figure 1). After training was completed, the ants were transferred to a linear test channel oriented in the same north–south direction. Control ants were trained along a linear path with the feeder 3 m to the north of the nest. After their release into the test channel the experimental ants ($n = 30$) ran much further in the northward direction than the control ants ($n = 30$) before they performed their first turn (Figure 1A, $p < 0.0001$). This result means that the 6U3 ants overshot the nest-to-feeder distance and headed for the U-turn as their first target.

In a second experiment, the ants were trained in a reversed, more demanding setting (3U6; Figure 1); the inbound ants now had to decide whether they should head for the U-turn or whether they should head for the nest now lying in the opposite direction of the U-turn. Only six of the 30 experimental ants directly ran off their home vector (as all control ants did); the remaining 80% of the experimental ants first headed for the fictive U-turn (Figure 1A; difference between control and test group, $p < 0.0001$). This clear-cut result again shows that even in the difficult 3U6 task the ants had acquired and used remarkable knowledge about their two-leg training path.

It is well known that *C. fortis* [6], as well as other species of ants [7–9], can attach local vectors to particular landmarks encountered *en route*. In an intriguing experiment, channel-bound flying honey bees were also shown to use local vectors attached to on-route visual signposts [10]. In our work, we tried to reduce the influence of landmarks by using linear channels. Hence, the landmark situation at the feeder, at the nest and in fact during the entire run was almost the same. The only visual irregularities were the food crumbs at the feeder position and an inconspicuous opening between the two channels at the U-turn. Both cues, of course, were missing in the test channel.