REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
03-28-2019	Performance/Technical	03-01-2013 - 02-28-2016

4. TITLE AND SUBTITLE

Defining factors that extend circadian entrainment capabilities of mammals

5a. CONTRACT NUMBER

5b. GRANT NUMBER

N00014-13-1-0285

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Michael Gorman

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, San Diego, Center for Circadian Biology
9500 Gilman Drive, Mail Code 0109
La Jolla, CA 92093-0109

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Office of Naval Research REG Office San Diego
140 Sylvester Road, Bldg. 140 Room 218
San Diego, CA 92106

10. SPONSOR/MONITOR'S ACRONYM(S)

ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER

N66018

12. DISTRIBUTION AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

See attached for full abstract - Both shift-work and jet-lag are national security concerns as a result of their effects on military personnel. Mice, like humans and all other mammals, exhibit robust daily rest/activity cycles that are regulated by a biological clock in the hypothalamus synchronized to the local environment by the light/dark cycle. Because the ability of light to reset the clock is limited, it takes several days for mammals to adjust to rapid travel across time-zones (i.e., jet-lag) or to alter circadian phase to accommodate night-time work schedules at substantial cost in productivity, safety and health. This project established that simple light manipulations allow extraordinary entrainment

15. SUBJECT TERMS

shift-work, jetlag, circadian disruption, fatigue, sleep, melatonin, gender

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Michael Gorman
U	U	U	SAR	11	19b. TELEPONE NUMBER *(Include area code)* (858) 822-2466

Final Technical Report Abstract

Mice, like humans and all other mammals, exhibit robust daily rest/activity cycles that are regulated by a biological clock in the hypothalamus synchronized to the local environment by the light/dark cycle. Because the ability of light to reset the clock is limited, it takes several days for mammals to adjust to rapid travel across time-zones (i.e., jet-lag) or to alter circadian phase to accommodate night-time work schedules at substantial cost in productivity, safety and health. Both shift-work and jet-lag are national security concerns with respect to military personnel. This project established that simple light manipulations allow extraordinary entrainment in mice to schedules that are or could be used by military personnel including 18 - 30 h days and rotating shift-work. Such manipulations minimize performance decrements associated with shift-work. Enhanced circadian flexibility is shown to be intrinsic to the circadian pacemaker in the brain and likely reflect dampening of molecular circadian oscillators. Gender, age and lighting parameters modulate circadian plasticity. The results clearly establish an unprecedented capacity of the circadian clock of mammals to permit sleep/rest at artificial schedules of great utility for military operations and suggest approaches for translation of this work from rodents to humans.

Key words: shift-work, jetlag, circadian disruption, fatigue, sleep, melatonin, gender

Michael R. Gorman
University of California, San Diego
N00014-13-1-0285
Defining factors that extend circadian entrainment capabilities of mammals

Abstract
Both shift-work and jet-lag are national security concerns as a result of their effects on military personnel. Mice, like humans and all other mammals, exhibit robust daily rest/activity cycles that are regulated by a biological clock in the hypothalamus synchronized to the local environment by the light/dark cycle. Because the ability of light to reset the clock is limited, it takes several days for mammals to adjust to rapid travel across time-zones (i.e., jet-lag) or to alter circadian phase to accommodate night-time work schedules at substantial cost in productivity, safety and health. This project established that simple light manipulations allow extraordinary entrainment in mice to schedules that are or could be used by military personnel including 18 - 30 h days and rotating shift-work. Such manipulations minimize performance decrements associated with shift-work. Enhanced circadian flexibility is shown to be intrinsic to the circadian pacemaker in the brain and likely reflect dampening of molecular circadian oscillators. Gender, age and lighting parameters modulate circadian plasticity. The results clearly establish an unprecedented capacity of the circadian clock of mammals to permit sleep/rest at artificial schedules of great utility for military operations and suggest approaches for translation of this work from rodents to humans.

Final Narrative Report

The Problem: As in nearly all animal species, humans evolved to behave productively during a particular fraction of the 24 h cycle (i.e., the day) and to rest during the remainder. The rest/activity cycle is coordinated by a circadian biological clock in the suprachiasmatic nuclei (SCN), and its phase is adjusted by the ambient cycle of light and dark. This creates a problem when activity must be extended beyond conventional daytime hours as required in myriad military contexts and in shift work. If voluntary activity is extended into the species-typical hours of rest *without* a corresponding shift in SCN phase, performance efficiency is substantially decreased [1] and multiple aspects of health and well being are compromised [2].

Unfortunately, the circadian clocks of mammals (humans and animal models) shift very incrementally and slowly. Exposure to natural lighting strongly cannot be avoided without great discipline, and any such exposure reinforces the typical circadian phase [3]. Fewer than 4% of permanent night shift-workers, a population most likely to show appropriate circadian adaptation, have corresponding phase adjustments of their biological clock [4]. This inevitable misalignment in shift-work between rest/activity scheduling and our internal biological clocks compromises military and industrial efficiency, public safety and worker health (i.e., cancer risk, metabolic disease, mood disorders, reproductive complications) at an estimated annual cost in the US of $200 billion [5]. Where vital functions must occur around the clock – security, medical care, transportation, delivery of essential services – this "anti-phase" problem requires a solution. It is of particular relevance in a national security context as military operations must be optimized for any time of day or night [6–9]. By devising strategies to enable flexible and rapid adjustment of circadian rhythms, we hope to mitigate these harms.

Promising Solutions: Work in my laboratory strongly suggested that rapid adjustment of circadian rhythmicity may be achieved through manipulation of pacemaker *waveform* – the shape of the 24 h oscillation – rather than simple manipulation of circadian *phase* per se. Research effort towards the latter strategy has dominated circadian biology to the near exclusion of the former. Unfortunately, this narrow focus on circadian phase has yielded little by way of practically implemented and effective strategies for meeting the needs of shift-workers [10].

Our focused interest on circadian *waveform* derives from series of studies in rodents demonstrating a surprising degree of pacemaker plasticity under unconventional lighting conditions [11,12]. Briefly, when maintained on a permissive 24 h light:dark:light:dark (LDLD) cycle, nocturnal rodents can be induced to re-organize their circadian timing systems such that they show night-typical levels of *activity* in each of the two daily dark periods. Likewise, they exhibit daytime patterns of *inactivity* during each of the two daily light periods. Called rhythm "bifurcation," this entrainment paradigm allows animals to express in each 24 h cycle two subjective days each lasting ~7-8 h and beginning 12 h apart and two subjective nights of ~ 4-5 h each, also 12 h apart [11,13–15].

Before this project began, we elaborated how rhythm bifurcation could theoretically be highly beneficial to humans [16]. In our proposed scheme, in every 24 h period a bifurcated human would exhibit two intervals of subjective day (characterized by high alertness) and two intervening intervals of subjective night (characterized by elevated melatonin and high sleep efficiency). One of two alert intervals can be entrained to occur during the natural day to coincide with business and family demands, whereas the second would be timed to occur to match work scheduled at night. Sleep would occur in two phases in-between. Critically, natural and artificial light would have complementary effects on maintaining this state. Our earlier paper [16]provides additional reasons why bifurcation may be plausibly expected in humans and illustrates how flexible such an entrainment regimen could be.

The completed project has yielded three main contributions described in more detail below. First, using bifurcation as a standard assay, we defined physiological, environmental and behavioral factors that modulate circadian plasticity. Second, and most exciting to us, we demonstrated that extraordinary entrainment is not particular to our bifurcation protocol. On the contrary, circadian plasticity can be generalized to a great variety of conditions of utility to military personnel and is not limited to the particular conditions under which it was discovered and optimized. Third, we have investigated neural mechanisms of bifurcation and enhanced circadian resetting.

Major findings of the sponsored project.

Bifurcation in T24 LDLD

- We identified critical extrinsic (e.g., lighting) and intrinsic (e.g., sex) factors that modulate the *induction* of bifurcation. Functionally relevant extrinsic factors include night lengths < 6 h; the presence of extremely dim illumination (< 0.1 lux, equivalent to dim moonlight) throughout all night phases; intensity of bright light during the day and availability of a running wheel. Intrinsic factors that influence bifurcation include sex and

age. Exposure to nightly melatonin was hypothesized to influence bifurcation but was shown to have no effect. The effects of photoperiod, gender, melatonin and age are illustrated in Figures 1 and 2. A manuscript with these and other results is in the final stages of preparation and will be submitted for publication in 2019.

- We demonstrated that bifurcation is maintained in conditions that are insufficient to induce it. Neither dim light nor short night duration is necessary to *maintain* bifurcated entrainment or other extraordinary entrainment conditions. A separate manuscript with these and other results is in the final stages of preparation and will be submitted for publication in 2019. Figure 3 illustrates months-long activity patterns of two mice -- one unbifurcated (right) and one induced to bifurcated (left) with short nights but subsequently maintained in a bifurcated state in non-inductive conditions.
- Dim light need not be continuously present throughout the night but can be intermittent. We do not anticipate publishing this result, but it informs our interest in translational studies we hope to conduct in humans and non-human primates.
- We have demonstrated using simple learning paradigms, that learning and memory are compromised by repeated phase-shifting as might occur in shift-workers but are protected from deficits by rhythm bifurcation. This work is summarized in the published paper by Harrison et al., 2015.

Extraordinary entrainment to other lighting conditions

Additionally, we have made several discoveries showing that bifurcation and dim light lead to extraordinary flexibility to other types of lighting schedules.

- Following bifurcation, mice can be readily entrained to non-24 h days. First, we have demonstrated the animals with a history of bifurcation will entrain to 30 h LDLD cycles, a result that is without precedent in mammals (at least as far as the quality of entrainment is concerned). The dependence of this behavior on bifurcation history and exposure to dim light is summarized in the 2016 publication by Harrison et al. in Scientific Reports and representative results are featured here in Figure 4. We have completed additional follow-up studies that demonstrate how entrainment to 30 h cycles can be used successfully to simulate rapidly delaying shift-work (starting 6 h later each day) interspersed with 24 h cycles to simulate a weekend on normal daylight hours. The latter project will be combined with two other models of shift-work in a manuscript that will be submitted soon.
- While our work or extraordinary entrainment evolved over time in the context of studies of bifurcation, we discovered unexpectedly that bifurcation was NOT always necessary for some forms of extraordinary entrainment. To induce bifurcation, mice require exposure to very dim light at night as opposed to complete darkness. To our surprise, this nighttime lighting alone, without prior bifurcation, also permits stable entrainment to non-24 h days. For example, mice with a conventional entrainment history to 24 h days can adapt nearly instantaneously to an 18 h day (**T18** LD13:5) if they are provided with dim nocturnal illumination equivalent in intensity to dim moonlight. In contrast, if the nights are completely dark -- as is conventional in circadian rhythms research -- mice cannot adapt to the 18 h cycle and instead drift with a rhythm not quite equal to 24 h. Entrainment to a 18 h day is equivalent to an advance of 6 h each and every day (Fig. 5)

and resembles a schedule that has been employed on some navy vessels. This form of extraordinary entrainment is fully described in Walbeek et al., 2017. That publication also establishes that bifurcation, without continuing dim light, permits the same entrainment. In follow-up studies, we have replicated the basic findings and additionally demonstrated that mice entrained to LD13:5 have hyper-resettable circadian clocks. A separate publication will result from these data, but we do not have an anticipated publication date because we may combine these data with other ongoing projects.

Mechanisms of extraordinary entrainment and resetting

Finally, we have characterized the mechanisms of bifurcation and extraordinary entrainment and extended studies to organ systems believed to play important roles with respect to circadian misalignment and poor health and performance. Key results are summarized in our recent paper (Noguchi et al., 2018).

- Bifurcation reduces the amplitude of expression of some clock genes in liver, lung and/or adrenal and renders some clock genes bimodal, but not all.
- Under the guidance of our Program Officer, LCDM Christopher Steele, we retooled the laboratory to conduct cellular imaging studies of the circadian pacemaker in the brain, the suprachiasmatic nuclei (SCN) using genetically altered mice that express a bioluminescent marker (PER2::LUC) of a key protein in the molecular clockwork. With this technology, we were able to evaluate whether enhanced plasticity in behavior would be mirrored in measures of established circadian tissues. Compared to non-bifurcated controls, bifurcation results in markedly stronger phase-resetting of SCN PER2::LUC rhythms by dissection stimulus, consistent with nearly instantaneous behavioral resetting in whole animals (Fig. 6). Other organs systems in the body showed varying degrees of modulation by bifurcation. But as a rule, increased resetting in a tissue was associated with reduced amplitude of clock gene expression in that tissue.
- Finally, using similar technologies, we developed the capacity to measure the entrainability of *in vitro* cultures of lung, liver and adrenal PER2::LUC rhythms using temperature pulses (data not shown).

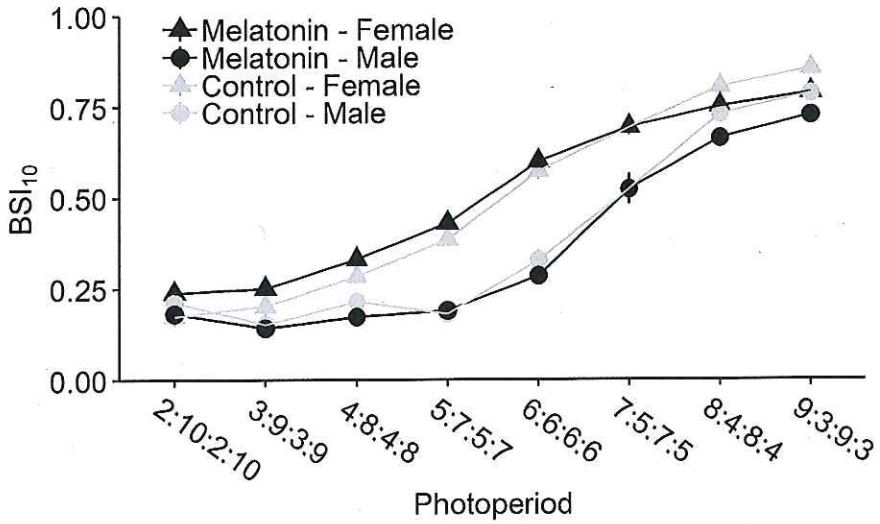

Figure 1. After extensive validation [17], an index of bifurcation (Bifurcation Symmetry Index, BSI) was established as a simple metric to enable robust statistical analysis of this complex behavioral entrainment condition. (The subscript denotes the number of cycles over which the measure was calcuated). This graph demonstrates that a) bifurcation is elicited preferentially by longer photophase/shorter scotophases; b) that female mice more readily exhibit bifurcated behavior than do males; and c) that melatonin has no effect on bifurcation.

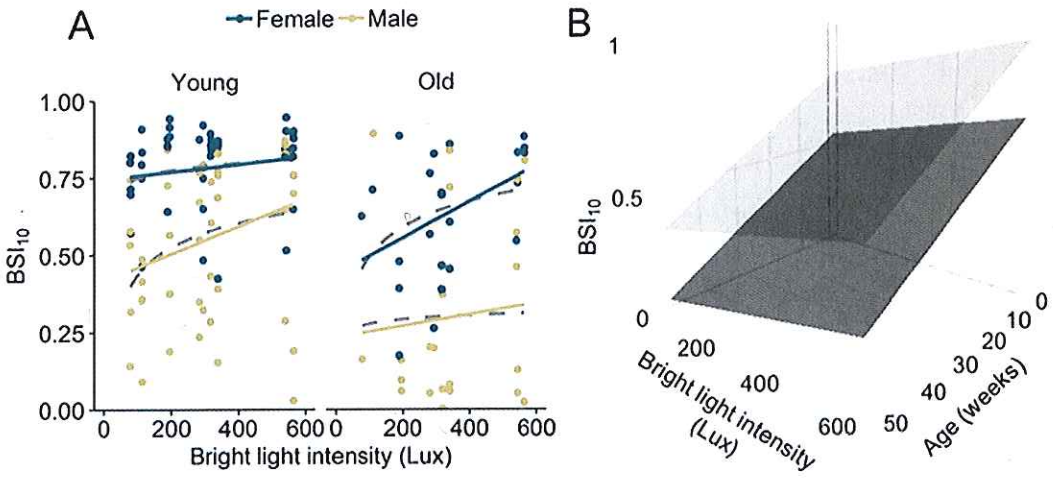

Figure 2. The figure above uses the same measure of bifurcation (BSI) to illustrate that a) female mice bifurcate more readily than do male mice; b) that younger mice bifurcate more readily than do older mice; and c) that bifurcation is more readily elicited when photophases are more brightly illuminated.

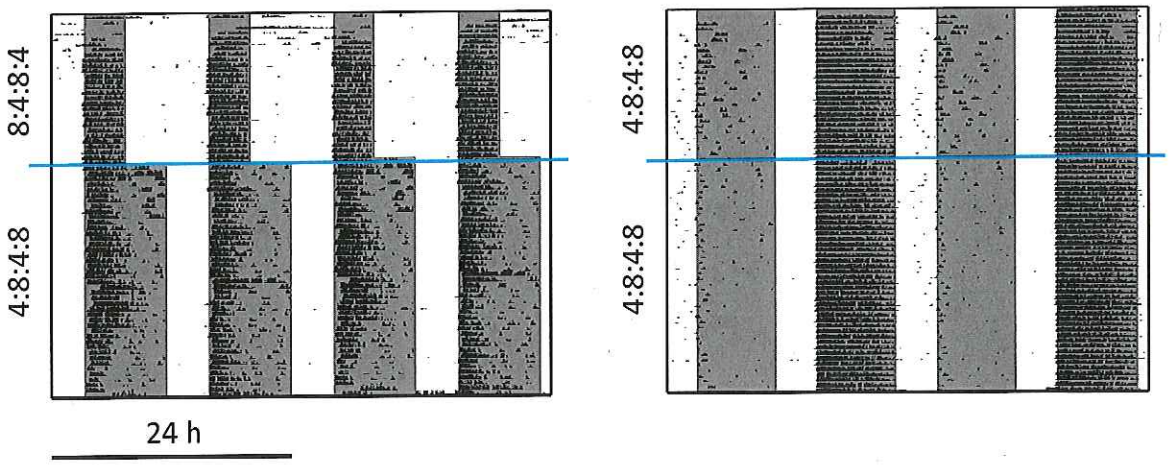

Figure 3. This figure depicts rest/activity rhythms of individual mice over several months to illustrate a bifurcated versus not-bifurcated entrainment pattern and the dissociation of light requirement for bifurcation induction versus maintenance. Each graph represents a doubled-plotted (48 h on x-axis) wheel-running actogram of an individual mouse maintained under T24 LDLD cycles for approximately 2 months. Dark shading represents times of darkness. In the left panel (top portion), the mouse was initially exposed to T24 LDLD8:4:8:4, which *induced* bifurcation as reflected in emergence of robust wheel-running activity in each of the dark phases. In contrast, the mouse from the right panel was exposed to T24 LDLD4:8:4:8 and did not bifurcate. Rather, activity was concentrated in only one of the two 8 h dark intervals. When the mouse on the left was exposed to these same T24 LDLD4:8:4:8 conditions (bottom portion), it *maintained* its bifurcated status. Thus, the two mice receive identical conditions in the latter portion of the experiment, but only one is bifurcated. Dim nocturnal illumination was present throughout.

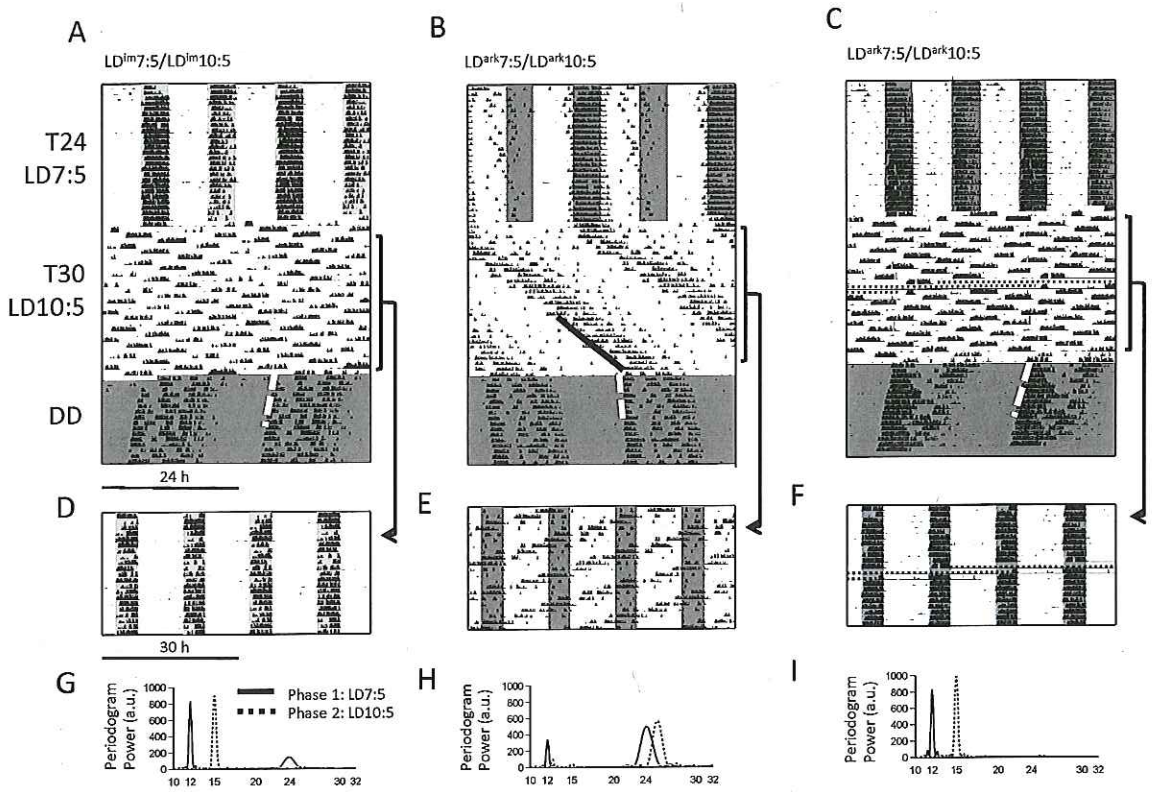

Figure 4. Double-plotted activity records of mice illustrating bifurcated entrainment to T24 LDLD and T30 LDLD conditions. Each record shows wheel-running activity collected over approximately 2.5 months. In A, the nights were dimly illuminated (<0.1 lux) and the mouse (like all others in the group) bifurcated, as evident by robust wheel-running occurring in each of the dark periods. In contrast, in B, the nights were completely dark and the mouse did not bifurcate. Instead, activity is strongly concentrated in just one of the two dark periods. Whereas the mouse in B illustrates the response of ~90% of mice exposed to completely dark nights in T24 LDLD, the mouse in C did bifurcate under such conditions. In the second phase of the study, mice were exposed to T30 LDLD (10 h of light, 5 h of dark, repeated). If previously bifurcated in T24 LDLD, mice will entrain to these T30 LDLD cycles. The actograms display the same data from this portion of the study both in 24 h (A-C) and 30 h (D-F) formats. The entrainment of mouse A is most clearly seen in the *modulo-30* plot (D) as activity closely aligns with all of the shaded dark periods. In the second mouse, failed entrainment is seen in poor alignment in the modulo-30 h plot (E). Additionally, in the modulo-24 h plot (B), a clear free-running period > 24 h is also clearly evident. The mouse that bifurcated with dark nights (C) also clearly entrains to T30 LDLD. The final portion of the actogram shows resumption of normal unbifurcated rhythms in constant darkness (DD). Lomb-Scargle periodograms (G-I) provide simple objective measures for quantitative analyses (not shown) of these entrainment behaviors. Thorough analysis of group data (not shown) clearly establish stable entrainment to 30 h LDLD cycles that becomes independent of exposure to dim nighttime lighting. **Note that following bifurcation, the T30 lighting regime enabled activity to be scheduled for any hour of the 24 h day. If not previously bifurcated, timing of activity was under the control of the endogenous circadian oscillator, not the lighting cycle.**

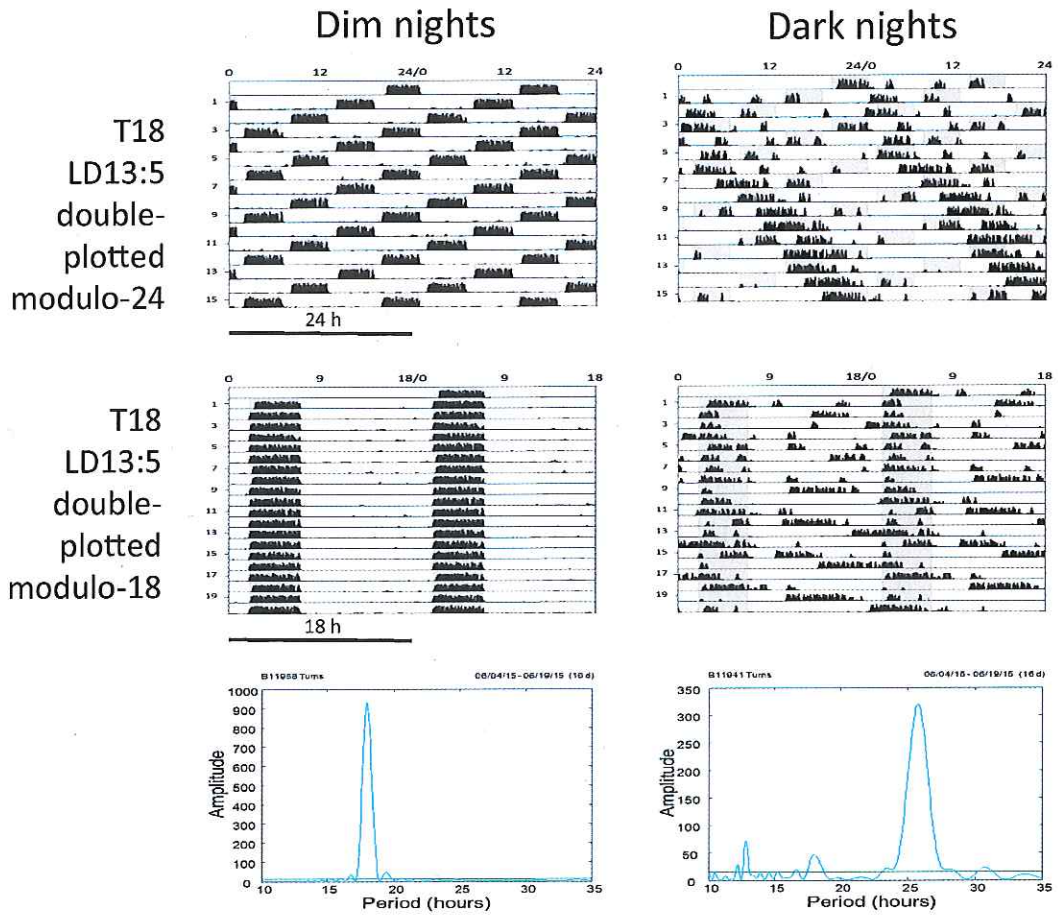

Figure 5. Mice can entrain their behavior to match an 18 h day (T18 LD cycle). Two weeks of wheel-running data are shown for two mice. Top panels use the conventional 24 h double-plotted actograms with shading used to indicate periods of darkness. In the middle rows, the same data are replotted "modulo-18 h." The mouse shown in the left column was exposed to dim nighttime illumination and is clearly entrained to 18 h as indicated by the vertical alignment of activity with the dark periods in the middle panel. The mouse in the second column, which was not exposed to dim nighttime illumination, is not entrained as reflected in the obvious free-running circadian rhythm with period > 24 h. In the middle row, it is additionally evident that the activity of this mouse is not limited to the dark periods occurring every 18 h. Periodogram analysis (bottom panels) quantitatively supports these conclusions. As in Figure 4, these results demonstrate that simple lighting manipulations can enable us to schedule rest/activity for any portion of the 24 h day (left) whereas standard conditions leave activity under the strong control of an endogenous circadian rhythm.

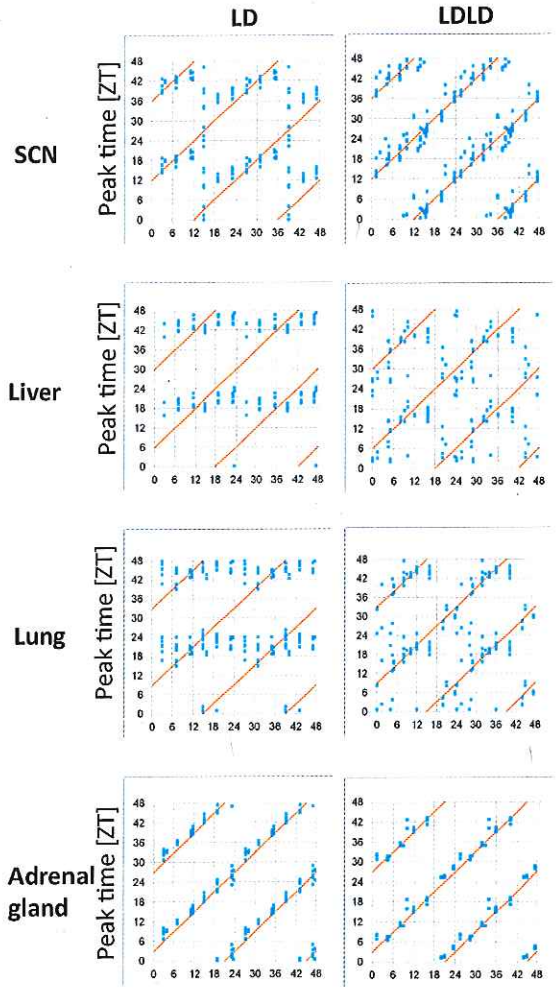

Figure 6. Bifurcation produces tissue-specific increases in phase-setting. In these experiments, tissues were collected at all different times of day from PER2::LUC mice and cultured *in vitro*. The process of dissection and establishment in culture medium is a stimulus that can reset the phase of the circadian clock in tissues. Blue dots represent peak phases in PER2::LUC expression of individual cultures. If phase is not reset by dissection, then the dots will fall along a horizontal line (i.e., the time of peak PER2::LUC phase will be determined by the prior lighting conditions under which the mice were entrained). If phase is strongly reset by dissection, then the dots will deviate from the horizontal line. In adrenal (bottom panel), for instance, the phase after dissection is linearly related to the time of dissection. This means that the dissection stimulus restarted the tissue at a particular phase. In SCN, liver and lung, the points deviate more from horizontal after bifurcated entrainment in LDLD than after non-bifurcated entrainment in LD. We can conclude that prior entrainment status affects the ability of SCN, lung and liver to be reset. These results closely mirror the increased reset-ability of behavioral rhythms.

Overall summary and naval relevance

We have achieved unprecedented control of the rest/activity of rodents by manipulating the nighttime lighting environment and bifurcation history. We are aware of no research program that has discovered any manipulation as simple as this for improving entrainment to non-conventional lighting conditions. We see at least three concrete examples of naval relevance as well as more general national security relevance.

1. Bifurcation in rodents is a rapidly induced, stable, flexible adjustment of the circadian pacemaker so that daytime physiology may be programmed to occur during both natural daylight hours and at night. A human with a bifurcated rhythm would be expected to work the night shift with the same alertness that is typically programmed during the day. The alternative forms of extraordinary entrainment (**T30-Bifurcation** and **T18**) have similar potential utility for scheduling alert activity across day and night. Moreover, it is expected that these entrainment regimens will protect against the health insults generated by chronic circadian misalignment.

2. Bifurcation in rodents essentially eliminates jet-lag [18]. A human with a similar circadian organization could be deployed to any time zone on earth and be expected to adjust rapidly to local time or, with continued controlled light exposure, be set to exhibit optimal alertness during any particular phase.

3. Bifurcation in rodents permits scheduling of rest/activity cycles at periods that are far from 24 h (e.g., 15 h, 18 h, 30 h). Until now, this flexibility is unprecedented in a mammal. Currently, littoral combat ships can be scheduled on 18 h days, but clocks are unable to adjust their circadian clocks to run at this period [19].

No patents or inventions resulted from this project.

Published papers supported by the project

Noguchi T, Harrison EM, Sun J, May D, Ng A, Welsh DK, et al. Circadian rhythm bifurcation induces flexible phase resetting by reducing circadian amplitude. European Journal of Neuroscience. 2018;doi: 10.1111/ejn.14086. [Epub ahead of print].

Harrison EM, Carmack SA, Block CL, Sun J, Anagnostaras SG, Gorman MR. Circadian waveform bifurcation, but not phase-shifting, leaves cued fear memory intact. Physiol Behav. 2017;

Walbeek TJ, Gorman MR. Simple Lighting Manipulations Facilitate Behavioral Entrainment of Mice to 18-h Days. J Biol Rhythms. 2017;32(4):309–22.

Harrison EM, Walbeek TJ, Sun J, Johnson J, Poonawala Q, Gorman MR. Extraordinary behavioral entrainment following circadian rhythm bifurcation in mice. Sci Rep. 2016;6.

Harrison EM, Gorman MR. Rapid Adjustment of Circadian Clocks to Simulated Travel to Time Zones across the Globe. J Biol Rhythms. 2015;30(6):557–62.

Manuscript supported by the project but not yet submitted for publication (results are available upon request).

Walbeek, TJ, Joye, DAM, Mishra, I & MR. Gorman. Influence of physiological, behavioral and environmental factors on circadian entrainment in mice. *In preparation.*

Sun, J, Farkas, AH, Joye, DAM & MR Gorman. Photoperiodic requirements for rhythm bifurcation and extraordinary entrainment after-effects in mice. *In preparation.*

Walbeek, TJ, Harrison, EM, Soler, RR & MR Gorman. Flexible entrainment increases alignment in real-world shiftwork schedules. *In preparation.*

Literature cited

1. Akerstedt T. Sleep Loss and Fatigue in Shift Work ahd SWD. Sleep Med Clin. 2009;4(2):257–71.
2. Costa G. The impact of shift and night work on health. In: Applied Ergonomics. 1996. p. 9–16.
3. Smith MR, Fogg LF, Eastman CI. Practical Interventions to Promote Circadian Adaptation to Permanent Night Shift Work: Study 4. J Biol Rhythms. 2009 Apr 1;24(2):161–72.
4. Folkard S. Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. Chronobiol Int. 2008 May;25(2):215–24.
5. Kerin A, Carbone J. Financial opportunities in extended hours operations: managing costs, ricks and liabilities. Lexington, MA: Circadian Technologies; 2003.
6. Hursh SR, Redmond DP, Johnson ML, Thorne DR, Belenky G, Balkin TJ, et al. Fatigue Models for Applied Research in Warfighting. In: Aviation Space and Environmental Medicine. 2004.
7. Caldwell JA, Mallis MM, Caldwell JL, Paul MA, Miller JC, Neri DF. Fatigue countermeasures in aviation. Aviation Space and Environmental Medicine. 2009.
8. Sanquist TF, Raby M, Forsythe A, Carvalhais AB. Work hours, sleep patterns and fatigue among merchant marine personnel. J Sleep Res. 1997;
9. Arulanandam S, Tsing GC. Comparison of alertness levels in ship crew. An experiment on rotating versus fixed watch schedules. Int Marit Health. 2009;
10. Smith MR, Eastman CI. Shift work: Health, performance and safety problems, traditional countermeasures, and innovative management strategies to reduce circadian misalignment. Nat Sci Sleep. 2012 Jan;4:111–32.
11. Gorman MR, Elliott JA. Entrainment of 2 subjective nights by daily light:dark:light:dark cycles in 3 rodent species. J Biol Rhythms. 2003;18(6):502–12.
12. Gorman MR, Elliott JA. Dim nocturnal illumination alters coupling of circadian pacemakers in Siberian hamsters, Phodopus sungorus. J Comp Physiol A Neuroethol Sensory, Neural, Behav Physiol. 2004;190(8).
13. Yan L, Silver R, Gorman M. Reorganization of suprachiasmatic nucleus networks under 24-h LDLD conditions. J Biol Rhythms. 2010;25(1):19–27.
14. Gorman MR. Exotic photoperiods induce and entrain split circadian activity rhythms in hamsters. J Comp Physiol - A Sensory, Neural, Behav Physiol. 2001;187(10).
15. Evans JA, Elliott JA, Gorman MR. Dynamic interactions between coupled oscillators within the hamster circadian pacemaker. Behav Neurosci. 2010;124(1):87–96.
16. Harrison EM, Gorman MR. Changing the waveform of circadian rhythms: Considerations for shift-work. Front Neurol. 2012;MAY(May):1–7.
17. Harrison EM, Walbeek TJ, Sun J, Johnson J, Poonawala Q, Gorman MR. Extraordinary behavioral entrainment following circadian rhythm bifurcation in mice. Sci Rep. 2016;6.
18. Harrison EM, Gorman MR. Rapid Adjustment of Circadian Clocks to Simulated Travel to Time Zones across the Globe. J Biol Rhythms. 2015;30(6):557–62.
19. Kelly TL, Neri DF, Grill JT, Ryman D, Hunt PD, Dijk DJ, et al. Nonentrained circadian rhythms of melatonin in submariners scheduled to an 18-hour day. J Biol Rhythms. 1999;