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14. ABSTRACT
The Center was part of the academic-industry Partners for Research Excellence and Transition (PRET) program of AFOSR. Its focus was on basic science discoveries of countermeasures that could be transitioned to Air Force to prevent cognitive and neurobehavioral performance impairments during transmeridian deployment, sustained operations and night operations. Basic clinical research undertaken in laboratories at the University of Pennsylvania School of Medicine (P.I. Dr. Dinges), and Brigham & Women's Hospital/Harvard Medical School (P.I. Dr. Czeisler), resulted in extensive new data on the performance-enhancing effects of the novel wake-promoting drug modafinil. The information acquired on modafinil were transitioned to and implemented by AF operations. These two laboratories also used study results and their mathematical modeling expertise to advance predictive modeling of human performance relative to sleep and circadian dynamics, including collaboration with AFRL and other laboratories engaged in computational modeling. The Center successfully achieved the PRET goal of transitioning basic science on development of wake-promoting drugs through creation and involvement of Hypnion Inc. (P.I. Dr. Edgar), a sleep-wake biotechnology company co-founded by Dr. Edgar. As part of the Center, Hypnion conducted screening of a range of drugs for sleep-wake effects and conducted a forward genetics-based novel drug target discovery program.

15. SUBJECT TERMS
Human performance, sleep deprivation, circadian rhythms, countermeasures, mathematical modeling, sustained operations, alertness, naps, modafinil, pharmacology, drug discovery

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2. OBJECTIVES

The primary research objective of this PRET Center is the basic science of development and assessment of countermeasures to prevent or reverse cognitive and neurobehavioral performance impairments during transmeridian deployment (jet lag), sustained operations (sleep deprivation), night operations, and 24-hr (shift work) operations that are essential for Air Force success during manned and unmanned (UAV) operations. Through research undertaken in laboratories at the University of Pennsylvania School of Medicine, Brigham and Women's Hospital/Harvard Medical School, and Hypnion, Inc., center investigators have made substantial progress on behavioral, technological, and pharmacological countermeasures for the biological limits imposed on human performance by sleep loss and the circadian system. PRET Center results to date demonstrate that the goal of optimizing human performance in the face of prolonged work demands is feasible with continued basic research on countermeasure development, and that the basic neurobehavioral systems involved in maintaining human performance in the present of sleep loss can be modeled mathematically.

Project I at the University of Pennsylvania School of Medicine (Dr. Dinges), has used randomized, double-blind, placebo-controlled trials involving intensive physiological and behavioral monitoring to evaluate the cognitive and neurobehavioral effects of the novel wake-promoting compound, modafinil, during simulated SUSOPS (88-hr sleep deprivation). Research projects conducted in this project examined the effects of modafinil (either 200mg per day or 400mg per day administered as a split does of 200mg every 12 hours) in comparison to, and in conjunction with a single 2-hour nap each day during this prolonged vigil, to determine if neurobehavioral functions can be optimized by combining countermeasures. These results for modafinil were also compared to results from previously completed PRET Center experiments on the effects of sustained low-dose caffeine and two 2-hr naps per day across 88-hours of simulated SUSOPS. Experiments at the University of Pennsylvania School of Medicine were complemented by research on the effects of chronic sleep restriction with and without naps; on factors that predict individual vulnerability to performance impairment due to sleep loss; on the effects of cognitive workload on sleep homeostatic drive; on the effects of different amounts of recovery sleep following periods of chronic restriction; on development of fatigue-monitoring technologies designed to track and enhance operator alertness; and on biothmathematical and computational modeling of performance during sleep deprivation. In the final year of the project experiments were undertaken on the neural bases of the effects of sleep deprivation on psychomotor vigilance performance.

Specific Aims for Project I:

1. Test the hypothesis that modafinil (Provigil®) at 200 mg given once every 24 hours combined with a 2 hour nap every 24 hours (12 hours apart from the modafinil administration), versus placebo with a 2 hour nap every 24 hours, reduces the rate of homeostatic decline in neurobehavioral functions across 88 hours of total sleep deprivation. This aim has been completed.

2. Test the hypothesis that 200mg modafinil (Provigil®) administered once every 12 hours (for a total of 400mg per 24 hours), versus placebo, reduces the rate of homeostatic decline in neurobehavioral functions across 88 hours of total sleep deprivation. This aim has been completed.
3. Development of mathematical models to accurately estimate cognitive performance during sleep deprivation and at an adverse circadian phase. This aim was completed during the past year via a series of papers on mathematical modeling of our experimental data.
4. Integrate the findings from this basic research with experimental results from our related scientific studies on dose-response effects of chronic sleep restriction; the stability of inter-individual vulnerability to cognitive impairment during sleep loss; and on development of fatigue-monitoring technologies designed to track and enhance operator alertness. This aim was completed.
5. Develop new data and establish the feasibility and potential of integrating novel techniques from cognitive neuroscience into the study how sleep loss affects brain functioning and cognitive performance. This aim was introduced and completed in the past year.

Project II–a. The goals of the project at Brigham and Women's Hospital/Harvard Medical School (Dr. Czeisler) are to conduct a clinical trial simulating the chronic effects of both repeated deployment across multiple time zones (i.e., jet lag) and extended duty hours requiring sleep deprivation in order to evaluate the effectiveness of modafinil as a countermeasure for alertness and performance impairment associated with sustained operations and circadian misalignment.

Specific Aims for Project II–a:

1. Test the hypothesis that the novel wake-promoting therapeutic modafinil reduces the rate of homeostatic decline of neurobehavioral functioning during 28.57 h of sustained wakefulness. This aim was completed in the past year.
2. Test the hypothesis that modafinil reduces the impairment of cognitive and neurobehavioral functioning associated with working out of phase with the endogenous rhythms responsible for promoting wakefulness. This aim was completed in the past year.
3. Test the hypothesis that modafinil given to promote sustained wakefulness will not disrupt sleep in sleep episodes scheduled to occur at all circadian phases. This aim was completed in this past year.
4. Test the hypothesis that daily modafinil treatment of acute sleep deprivation and chronic transmeridian travel will be well tolerated. This aim was completed in the past year.

Project II–b The goals of the project at Brigham and Women's Hospital/Harvard Medical School (Dr. Klerman) are to develop biomathematical models of the regulation of subjective alertness and cognitive performance by homeostatic (sleep/wake) and circadian systems and their interaction, to provide a predictive tool of human performance over extended-durations. The research effort also sought to further develop and validate mathematical models of neurobehavioral functions; to incorporate

into the models the effects of caffeine, naps and modafinil on human alertness and performance; and to provide the Air Force with a user-friendly Performance Simulation Software package that can be used in the field, as well as with specific recommendations as to the optimal use of light, caffeine, naps and modafinil as countermeasures to the impairment in neurobehavioral functions induced by sleep deprivation and circadian misalignment.

Specific Aims for Project II–b:

1. To provide AFOSR with user-friendly Performance Simulation Software of refined mathematical models that accurately predicts the homeostatic (sleep/wake) and circadian regulation of human subjective alertness and cognitive throughput during sleep deprivation and circadian misalignment. This aim was completed in the past year.
2. To provide AFOSR with user-friendly Performance Simulation Software of validated using data from sleep deprivation studies that were initiated across the full circadian cycle, and to provide AFOSR with recommendations for the use of light as a countermeasure to the impairment caused by jet lag and SUSOPS.` This aim was completed in the past year.
3. To provide AFOSR with user-friendly Performance Simulation Software that incorporates the effects of caffeine on human neurobehavioral function, and to provide AFOSR with recommendations for the use of caffeine as a countermeasure to the impairment caused by jet lag and SUSOPS.
4. To provide AFOSR with user-friendly Performance Simulation Software that incorporates the effects of naps of different durations on human neurobehavioral function, and to provide AFOSR with recommendations for the use of naps as a countermeasure to the impairment caused by jet lag and SUSOPS.
5. To use model simulations and data collected in a previous study on the effects of modafinil in a comparison of the use of light, caffeine, naps and modafinil as countermeasures to the impairment caused by sleep deprivation and circadian misalignment.

Project III The goals of research at Hypnion, Inc. (Dr. Edgar) are to utilize the comprehensive comparison of wakefulness-promoting therapeutics and their interaction with sleep homeostasis in animal models, and to identify those compounds that are most promising as safe and effective ways to maintain human performance during prolonged Air Force operations. Dr. Edgar has previously performed basic research that identified modafinil as a prime candidate for human trials (projects I and II-a). Research in project III evaluates the effects on sleep and waking of acute and chronic modafinil use and its potential interactions with other wake-promoting compounds, investigates physiological determinants of wake-promoting efficacy, and explores the wake promoting benefits of a family of novel H_3 receptor antagonists.

Specific Aims for Project III:

1. Test the hypothesis that acute low-dose modafinil interacts synergistically with prototypical stimulants (caffeine, amphetamines) to produce heightened wakefulness. This aim has been completed.

2. Test the efficacy of wake-promoting compounds after acute sleep deprivation. This aim was completed.
3. Test the hypothesis that sustained modafinil-induced wakefulness will not result in precipitous hypersomnolence. This aim was completed.
4. Test the hypothesis that acute and sustained H_3 histaminergic autoreceptor antagonist treatment will promote wakefulness without subsequent and precipitous hypersomnolence, and to compare the relative efficacy of these compounds with other wake-promoting agents (modafinil, methamphetamine, pemoline) as a function of prior sleep loss. This aim was completed.

3. STATUS OF EFFORT

A. University of Pennsylvania (Project 1):
All specific aims for Project I were completed. In the period covering 9/1/04 -8/31/05, we completed Specific Aim 5 by performing a study on the neural basis of the Psychomotor Vigilance Test (PVT) during sleep deprivation, using functional magnetic resonance imaging (fMRI) (Drummond et al., The neural basis of the PVT, Sleep 28(9): 2005).

In the funding the period of the grant (2000-2005), we completed more than 550 24-hour protocols on grand total of N=50 subjects (11 days per subject) studied in the General Clinical Research Center at the Hospital of the University of Pennsylvania. This concluded data collection on two double-blind, placebo-controlled, randomized, parallel-groups experiments on modafinil effects of modafinil administration on cognitive, neurobehavioral, physiological, and clinical functions during simulated sustained operations (88-hour period of 0 to 2 hour sleep a day. Neurobehavioral data extraction (cognitive performance and mood assessments) and physiological sleep scoring were complete, along with data analyses.

B. Brigham & Women's Hospital/Harvard Medical School (Project II-a):
All specific aims for Project II-a were completed. During the 5-yerar period of the grant, a total of 550 subject-days of inpatient recording on the Intensive Physiological Monitoring Unit of the General Clinical Research Center at the Brigham & Women's Hospital. This represents a total of N=18 completed subjects and concludes subject enrollment for this protocol. The data collected during the 31-day study include: pre-study wake-sleep actigraphy and light exposure recording; minute-by-minute samples of core-body temperature; hourly blood plasma samples for assessment of hormones; neurobehavioral testing including reaction time (psychomotor vigilance task), mathematical processing (addition task), working memory (digit symbol substitution task), and tracking every two hours; polysomnographic recordings of sleep periods; daily assessments of sleep quality using subjective questionnaires; daily waking EEG and EKG recordings; and urine samples collected every three hours during waking periods. In total 17 of 19 subjects who were enrolled completed the study. One additional subject withdrew after completing approximately three-quarters of the protocol because of illness in a family member. This subject's data have been used for analysis.

Specific aims 1 and 2 were completed for **Project II-b**. For specific aim 3, a standardized analysis procedure was developed for all the neurobehavioral data collected within the Division of Sleep Research at the Brigham and Women's Hospital. To insure that these standards are carefully met, we have developed specialized data-analysis software for each neurobehavioral test currently conducted. We applied these criteria to all of the subjective alertness tests (visual analog scale and Karolinska Sleepiness Scale), cognitive throughput tasks (addition test, digit-symbol substitution task) and psychomotor vigilance tests conducted during the Division's previous PRET study investigating the effects of caffeine on neurobehavioral function. We have written data analysis programs in SAS to separate the homeostatic and circadian components of each of these tasks as well as the interactions of these components. For specific aim 3, we have finished preparing the data for analyses and have been unblinded to the caffeine/placebo status of each subject. We have mathematically analyzed the shapes of the resultant curves to determine the magnitude and nature of the effects of caffeine on the components of our neurobehavioral model. We have also added the KSS and DSST measures to CPSS. We have added the effects of caffeine to the mathematical model. We have also added the circadian aspect of sleep inertia to the model using data from the placebo condition of the caffeine study. Specific aims 4 and 5 were not completed since the data were not received before the end of the project period. We, however, added a non-photic component to the model. The manuscript detailing this work has been submitted for publication.

C. Hypnion (Project III):

All specific aims for Project III were completed during the 5-year period of the grant. The research led to a number of important developments and accomplishments that have lead us closer to identifying the next-generation of wake-cognition therapeutics. Hypnion secured second tranche Series-B funding and for the first-time advanced compounds into clinical trials for pharmacokinetic assessment. In 2004, Hypnion was judged one of the 100 "most influential" biotechnology companies in the world by *Acumen Journal*, and continues to receive accolades from the investment community and popular press. Hypnion continues to combine significant venture financing with AFOSR investment in wake-promoting therapeutic discovery. Hypnion information scientists, programmers, and database developers continued to refine the HypNET™ sleep-wake pharmacology database, last year adding a novel off-line EEG QC and spectral analysis software technology (ReSCORE™) to its discovery research armamentarium. Hypnion's IT team also have initiated a new software development initiative to enhance SCORE-2000™. Efforts are underway to enable SCORE-2000™ with real-time automated sleep deprivation capabilities utilizing a novel adaptive segmentation approach designed by Dr. Edgar. This technology is vital to ongoing progress in wake-promoting therapeutic drug discovery as the lead-optimization of a compound depends heavily upon efficacy in sleep-deprived animals. Hypnion's Life Sciences team performed comprehensive studies designed to evaluate the role of the adenosine A1 receptor in mediating physiological sleepiness. Since more than 90% of caffeine's wake-promoting efficacy is lost with only moderate (e.g., 5-hour) sleep deprivation in rats, studies were designed to determine if this is a general phenomenon of waking mediated specifically by the A1 receptor. Since caffeine increases central

neuronal excitability through antagonism of multiple receptor systems (A1, A2a, ryanadine, PDE), it is plausible that the A1 receptor is not the dominant determinant of physiological sleepiness, possibly explaining why dopamine transporter inhibitors showed additive but not synergistic interaction with caffeine or highly selective A1 antagonists (PRET activity reported last year).

4. ACCOMPLISHMENTS/NEW FINDINGS

A. Accomplishments/New Findings at University of Pennsylvania (PENN):
Two large-scale randomized, double-blind, placebo-controlled, parallel-groups experiments were completed on modafinil (involving a total N=50 subjects studied for 550 days in the laboratory). These experiments investigated the effectiveness of modafinil administration in reversing the detrimental effects of accumulated sleep loss during 88 hours of simulated sustained operations. In experiment 1 we examined the effects of 200mg modafinil per day, administered at 1200h, combined with a daily 2h nap at 0245h versus placebo plus a daily 2 hour nap at 0245h across 88 hours of SUSOPS. In experiment 2 we examined the effects of a split dose of 400mg modafinil per day (200mg at 1200h and 200mg at 0000h) versus placebo across 88 hours of SUSOPS. Data analyses from both experiments indicate positive effects of modafinil administration during 88 hours of simulated SUSOPS in reducing the cognitive deficits associated with extended hours of wakefulness and circadian phase. Using rate of change (β) for average daily outcomes across the 88h sleep deprivation period, a positive effect of modafinil administration, relative to placebo was observed for a range of neurocognitive tasks and a smaller number of subjective scales.

PENN—Experiment 1: 200mg modafinil/24h (1200h) vs. placebo during 88 hours of partial sleep deprivation (2-hr nap per day)

In experiment 1, comparison of measures from the post-drug administration period (1200hr–0200hr each day) revealed a positive effect of modafinil for psychomotor vigilance lapses ($P = 0.020$), [the primary performance outcome], fastest reaction times on the PVT ($P = 0.002$), critical tracking performance ($P = 0.003$), time estimation ($P = 0.044$), addition-subtraction task performance ($P = 0.046$), with a trend for probed recall memory performance ($P = 0.055$) (see Table 1). Neither digit symbol substitution performance ($P = 0.108$) nor psychomotor vigilance response errors of commission ($P = 0.261$) were significantly affected by drug, although in both cases slope differences were in the direction of improvement by modafinil. Comparisons following the nap period revealed that only time estimation performance was different between placebo and modafinil groups ($P = 0.048$), in the direction of better performance with modafinil. In contrast, modafinil administration at 1200h with a nap at 0245h had little effect on subjective assessment of sleepiness, fatigue and mood (Table 2). Modafinil significantly reduced physical exhaustion ratings ($P = 0.037$) and attenuated the decline in subjective vigor ($P = 0.026$) across the 88h, with a trend for improvement in tiredness ($P = 0.081$), and alertness ($P = 0.105$) ratings with relative to placebo. Modafinil had no significant effects on ratings of sleepiness, mental exhaustion, or fatigue following administration, and no effects on the post-nap period (0600hr-1200hr) slopes for any of the subjective outcomes.

The effects of a single daily 200mg dose of modafinil are illustrated in the temporal profiles of psychomotor vigilance lapses (Fig. 1a) and subjects' ratings of physical exhaustion (Fig. 1b) across the 88-hour experimental period. Subjects receiving placebo experienced a steady increase in the occurrence of vigilance lapses across the 88-hour experimental period, as cumulative sleep loss increased, while still showing the expected circadian modulation of performance. In contrast, subjects receiving modafinil showed a marked reduction in the occurrence of vigilance lapses during each post-drug period. Comparisons of PVT performance lapses between the modafinil and placebo groups on each day during the post-drug period from 1200h–0200h (1200h–2200h on the final day) revealed no significant differences prior to the first pill administration (i.e., 4h–20h time in the experimental period; $t = -1.63$, $P = 0.119$); but did reveal significant

Table 1. Experiment 1: Adjusted means (± s.e.m.) for rate of change in neurobehavioral performance outcomes across 88h of sleep deprivation with a 2h nap each 24h. Data from post-drug administration periods (1200hr–0200hr) for modafinil (200mg/24h) and placebo groups.

Performance variables	PLACEBO β[A]	MODAFINIL β	Curvature (θ)	P[B]
Psychomotor vigilance lapses[C]	2.84 ± 0.51	0.85 ± 0.56	1.1	0.020
Fastest reaction times (PVT)	11.61 ± 1.86	1.38 ± 2.03	0.6	0.002
Response errors (PVT)	0.27 ± 0.38	–0.40 ± 0.41	0.3	0.261
Probed recall number correct	–0.51 ± 0.12	–0.13 ± 0.13	0.4	0.055
Digit symbol number correct	–2.19 ± 0.45	–1.01 ± 0.50	0.9	0.108
Addition-subtraction correct/ time	–0.42 ± 0.18	0.15 ± 0.19	0.7	0.046
Critical tracking control failures	3.09 ± 0.50	0.45 ± 0.55	0.6	0.003
Time estimation accuracy	2.07 ± 0.82	–0.68 ± 0.90	0.6	0.044

[A]These values represent the group-mean rates of change β in the mixed-effects regression model of the form $\beta \bullet t^{\theta}$, where θ is the curvature parameter for time, and *t* represents time in days.
[B]*P* values are for testing the hypotheses that mean rates of change differed between subjects randomized to modafinil vs. placebo, controlling for baseline and age.
[C]Primary outcome measure; statistically significant after Bonferroni correction ($\alpha = 0.025$).

Table 2. Experiment 1: Adjusted means (± s.e.m.) for rate of change in subjective assessment outcomes across 88h of sleep deprivation with a 2h nap each 24h. Data from post-drug administration periods (1200hr–0200hr) for modafinil (200mg/24h) and placebo groups.

SUBJECTIVE RATINGS	PLACEBO β[A]	MODAFINIL β	Curvature (θ)	P[B]
Karolinska Sleepiness Scale[C]	0.97 ± 0.17	0.67 ± 0.19	0.8	0.270
Physical exhaustion rating	6.17 ± 0.71	3.75 ± 0.77	0.8	0.037
Mental exhaustion rating	4.00 ± 0.72	3.77 ± 0.79	1.0	0.839
Tiredness rating	5.76 ± 0.63	3.99 ± 0.69	0.8	0.081
Stanford Sleepiness Scale	0.61 ± 0.12	0.37 ± 0.13	0.9	0.196
Vigor from POMS	–3.16 ± 0.46	–1.47 ± 0.51	0.5	0.026
Fatigue from POMS	0.77 ± 0.24	0.91 ± 0.26	1.4	0.700
Alertness post-test-bout	0.25 ± 0.06	0.07 ± 0.07	0.4	0.105

[A]These values represent the group-mean rates of change β in the mixed-effects regression model of the form $\beta \bullet t^{\theta}$, where θ is the curvature parameter for time, and *t* represents time in days.
[B]*P* values are for testing the hypotheses that mean rates of change differed between subjects randomized to modafinil vs. placebo, controlling for baseline and age.
[C]Primary outcome measure; statistically significant after Bonferroni correction ($\alpha = 0.025$).

differences on each day of pill administration (28h–42h; t = –3.51, P = 0.004; 52h–66h; t = –2.76, P = 0.016; 76h–88h; t = –2.26, P = 0.037).

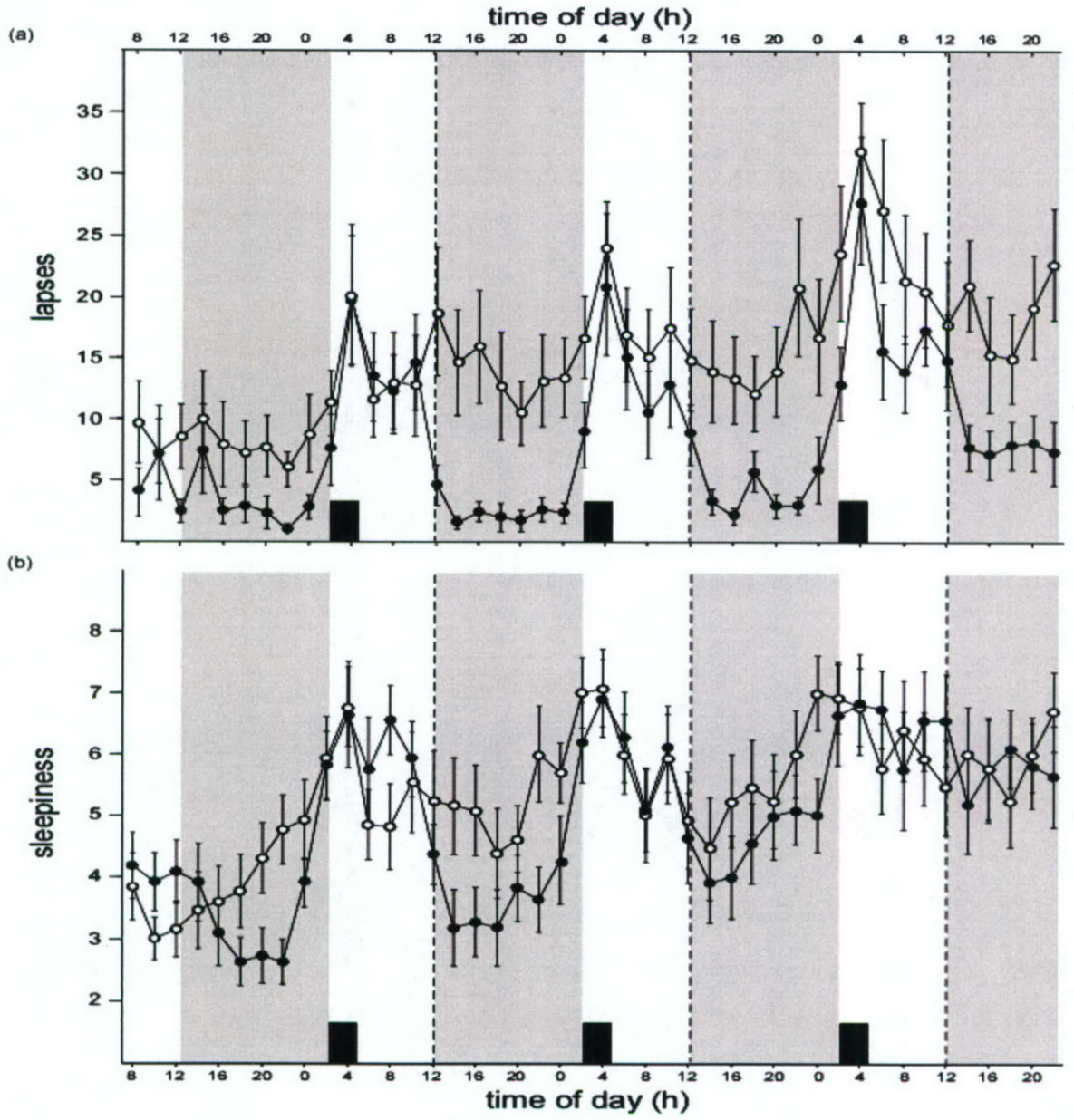

Figure 1. Experiment 1: Lapses in psychomotor vigilance performance (a) and sleepiness ratings from the Karolinska Sleepiness Scale (b) throughout 88h of simulated SUSOPS with 2h nap opportunities every 24h, and modafinil (200mg/24h) or placebo administration. Performance levels and sleepiness ratings (mean ± SEM) for subjects randomized to modafinil administration are shown as closed circles; equivalent outcomes for subjects randomized to placebo are shown as open circles. Time of day is represented on the top and bottom abscissas. Times subjects were allowed a 2h nap opportunity each 24h (0245hr–0445hr) are shown as solid black boxes. Times at which modafinil (200mg) or placebo were administered in double blind fashion are shown as dashed vertical lines (i.e., at 1200hr each day following the first night of sleep limited to 2h). Shaded (gray) areas show the post-drug administration periods used to test the hypothesis that modafinil would reduce both PVT lapses of attention and subjective sleepiness (KSS) relative to placebo.

Modafinil had no appreciable physiological side effects in the post-drug administration period (Table 3). A drug by nap interaction for heart rate ($F_{3,46} = 3.92$, $P = 0.014$) appeared to be due to a significant difference between modafinil and placebo groups at baseline, prior to drug administration. There were trends for modest elevations of core body temperature ($P = 0.060$) and plasma noradrenaline ($P = 0.073$) by modafinil. No significant effects between modafinil and placebo were found for circulating cortisol levels; melatonin levels; physical activity mean or variability; or any nap polysomnographic outcome.

Table 3. Experiment 1: Effects of modafinil (200mg/24h) relative to placebo on physiological variables across 88hr of sleep deprivation with a 2h nap each 24h. Data from the post-drug administration periods (1200hr–0200hr).

	Main Effect: DRUG			Interaction: DRUG X NAP		
Physiological variable	**DF**	**F**	**P***	**DF**	**F**	**P***
Core body temperature†	12	4.32	0.060	3, 37	0.70	0.557
Plasma cortisol	18	1.29	0.271	3, 57	2.01	0.122
Plasma melatonin	18	1.83	0.193	3, 57	1.75	0.166
Plasma noradrenaline	18	3.63	0.073	3, 57	0.94	0.425
Heart rate	16	0.11	0.748	3, 46	3.92	0.014
Heart rate variability	16	0.58	0.457	3, 46	1.33	0.275
Physical activity	20	0.28	0.604	3, 63	0.57	0.639
Activity variability	20	0.08	0.776	3, 63	0.79	0.503
Sleep variable						
Total sleep time	22.1	1.82	0.192	2, 41.9	1.71	0.193
Sleep latency	22.3	0.93	0.645	2, 42.0	2.09	0.137
Sleep efficiency	22.8	2.63	0.119	2, 42.3	1.44	0.247
Amount of stage 1 sleep	19.7	0.04	0.840	2, 39.5	0.83	0.444
Amount of stage 2 sleep	19.9	2.59	0.123	2, 39.7	0.67	0.516
Amount of SWS	23.0	0.34	0.564	2, 42.1	1.54	0.227
Amount of REM sleep	23.7	0.19	0.669	2, 43.0	0.29	0.752
Wake after sleep onset	24.1	1.59	0.220	2, 43.3	1.93	0.158

*P values are for testing the hypotheses that variables differed between subjects randomized to modafinil vs. placebo after controlling for age.
†Core body temperature data was available for only a subset of subjects (n=15)

The symptom complaint survey completed at the end of each neurobehavioral test bout throughout the 88h period of SUSOPS revealed a number of adverse experiences associated with modafinil administration (Table 4). Relative to placebo, subjects receiving modafinil had increased reports of headache ($P = 0.018$) and excitement ($P = 0.019$), with trends for increased difficulty concentrating and giddiness. All experiences reported were rated very low to moderate intensity.

In summary, relative to placebo, 200 mg modafinil at 12:00 hr daily across 88 hours of simulated SUSOPS significantly improved cognitive performance on most tasks, with less consistent effects on subjective assessments. There were few effects of modafinil

administration on sleep structure during the naps, or on physiological variables (endocrine measures, core body temperature, heart rate), or on adverse experiences.

Table 4. Experiment 1: Incidence of adverse experience reports during 88h of sleep deprivation with 2h nap opportunities every 24h for modafinil (200mg a 1200h) and placebo groups.

	% Subjects reporting		
Adverse Experience	**Modafinil***	**Placebo***	**P value†**
	n = 11	n = 13	
Body			
Headache	54.5	7.7	0.018
Ringing in the ears [a]	40.0	0.0	ns
Upset stomach/bowel	36.4	15.4	ns
Itchy skin	27.3	23.1	ns
Back ache/pain	18.2	0.0	ns
Muscle ache/pain	18.2	15.4	ns
Feeling too hot	18.2	0.0	ns
Joint ache/pain	9.1	15.4	ns
Feeling too cold	9.1	15.4	ns
Nervous System			
Tiredness (more than usual)	81.8	76.9	ns
Difficulty concentrating	72.7	30.8	ns
Difficulty remembering	54.5	30.8	ns
Irritability	36.4	30.8	ns
Feeling confused	36.4	15.4	ns
Excitement (more than usual)	55.0	0.0	0.019
Giddiness [b]	33.3	0.0	ns
Feeling anxious	18.2	15.4	ns
Sadness	18.2	15.4	ns
Worried [b]	16.7	25.0	ns
Dizziness [a]	0.0	20.0	ns

*Percentage of subjects in each condition who indicated they experienced a given symptom during the 30 neurobehavioral testing periods (every 2 hours) for the period from administration of the pill at 1200h on day 2 of the 88-hour protocol, to the end of the 88-hour period.

†P values are for the log rank $\chi 2$ used to test the hypothesis that the incidence of adverse experiences differed between subjects randomized to modafinil versus placebo

[a]Data available on only n = 5 subjects randomized to modafinil and n = 5 to placebo.

[b]Data available on only n = 8 subjects randomized to modafinil and n = 6 to placebo.

PENN—Experiment 2: 400mg modafinil/24h vs. placebo during 88 hours total sleep deprivation

Experiment 2 consisted of 400mg modafinil per day (administered in split doses every 12 hours) was compared to placebo for effects on cognitive, neurobehavioral and physiological measures across each 24h period for the 88 hours. Positive effects of modafinil were found for psychomotor vigilance lapses (P = 0.0009)—the primary performance outcome—as well as for fastest reaction times on the PVT (P = 0.048),

addition-subtraction task performance (P = 0.014), digit symbol substitution performance (P = 0.013), with a trend for time estimation accuracy (P = 0.080) (see Table 5). Neither probed recall memory performance (P = 0.885) nor critical tracking performance (P = 0.669) were significantly affected by drug, although in both cases slope differences were in the direction of improvement by modafinil. In contrast, 200mg modafinil administration at 1200h and at 0000h (total 400mg/24h) had fewer effects on subjective assessments of sleepiness, fatigue and mood (Table 6). Modafinil significantly increased alertness post test bout (P=0.016), with a trend for reduced fatigue (POMS fatigue subscale) (P=0.052).

Table 5. Experiment 2: Adjusted means (± s.e.m.) for rate of change in neurobehavioral performance outcomes across 88h of sleep deprivation. Data from 24hr periods for modafinil (400mg/24h) and placebo groups.

Performance variables	PLACEBO β[A]	MODAFINIL β	P[B]
Psychomotor vigilance lapses[C]	4.89 ± 0.60	2.50 ± 0.53	0.009
Fastest reaction times (PVT)	14.72 ± 2.29	8.12 ± 2.02	0.048
Probed recall number correct	-0.64 ± 0.09	-0.62 ± 0.08	0.885
Digit symbol number correct	-4.28 ± 0.63	-1.91 ± 0.56	0.013
Addition-subtraction correct/ time	-0.86 ± 0.18	-0.19 ± 0.16	0.014
Critical tracking control failures	3.12 ± 0.67	2.73 ± 0.59	0.669
Time estimation accuracy	1.81 ± 0.49	0.57 ± 0.44	0.080

[A]These values represent the group-mean rates of change β in the mixed-effects regression model of the form $\beta \bullet t^{\theta}$, where θ is the curvature parameter for time, and *t* represents time in days.
[B]*P* values are for testing the hypotheses that mean rates of change differed between subjects randomized to modafinil vs. placebo, controlling for baseline and age.
[C]Primary outcome measure; statistically significant after Bonferroni correction (α = 0.025).

Table 6. Experiment 2: Adjusted means (± s.e.m.) for rate of change in subjective assessment outcomes across 88h of sleep deprivation. Data from 24h periods for modafinil (400mg/24h) and placebo groups.

Subjective ratings	PLACEBO β[A]	MODAFINIL β	P[B]
Karolinska Sleepiness Scale[C]	1.94 ± 0.16	1.89 ± 0.14	0.811
Physical exhaustion rating	-11.01 ± 1.24	-7.84 ± 1.08	0.091
Mental exhaustion rating	9.44 ± 1.00	7.42 ± 0.87	0.175
Tiredness rating	10.75 ± 1.22	8.58 ± 1.05	0.233
Stanford Sleepiness Scale	1.16 ± 0.13	1.15 ± 0.11	0.978
Vigor from Profile of Mood States	-3.66 ± 0.36	-2.80 ± 0.32	0.096
Fatigue from Profile of Mood States	3.50 ± 0.45	2.24 ± 0.40	0.052
Alertness post-test-bout	0.36 ± 0.08	0.08 ± 0.07	0.016

[A]These values represent the group-mean rates of change β in the mixed-effects regression model of the form $\beta \bullet t^{\theta}$, where θ is the curvature parameter for time, and *t* represents time in days.
[B]*P* values are for testing the hypotheses that mean rates of change differed between subjects randomized to modafinil vs. placebo, controlling for baseline and age.
[C]Primary outcome measure; statistically significant after Bonferroni correction (α = 0.025).

The effects of 2 x 200mg doses of modafinil every 12 hours are illustrated in the temporal profiles of psychomotor vigilance lapses (Fig. 2a) and subjects' ratings of physical exhaustion (Fig. 2b) across the 88-hour experimental period. Subjects receiving placebo experienced a steady increase in the occurrence of vigilance lapses across the 88-hour experimental period, as cumulative sleep loss increased, while still showing the expected circadian modulation of performance. In contrast, subjects receiving modafinil showed a marked reduction in the occurrence of vigilance lapses during each post-drug period.

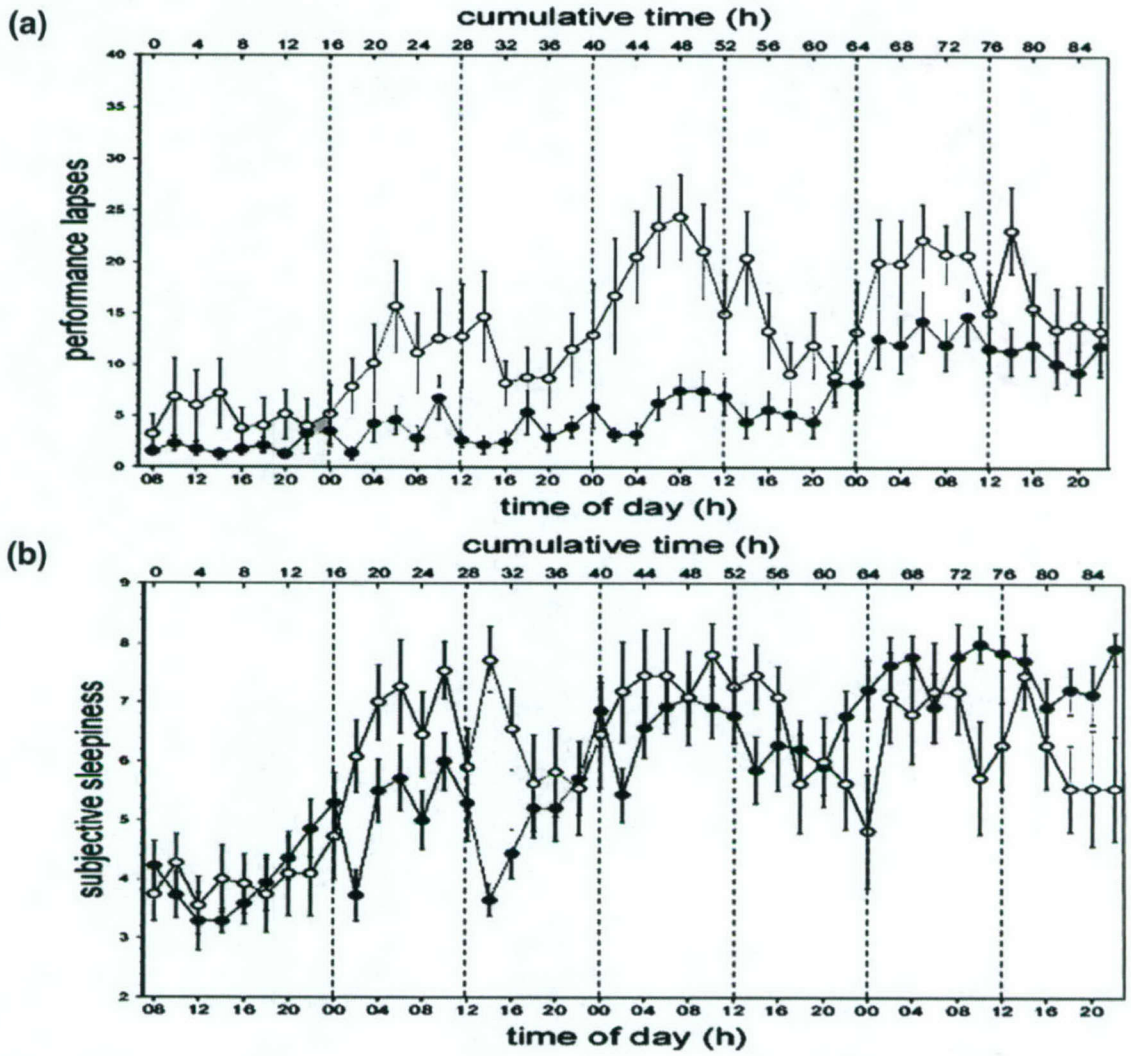

Figure 2. Experiment 2: Lapses in psychomotor vigilance performance (a) and sleepiness ratings from the Karolinska Sleepiness Scale (b) throughout 88h of continuous wakefulness (i.e., simulated SUSOPS) with modafinil (200mg/12h) or placebo administration. Performance levels and sleepiness ratings (mean ± SEM) for subjects randomized to modafinil administration are shown as closed circles; equivalent outcomes for subjects randomized to placebo are shown as open circles. Time of day is represented on the top and bottom abscissas. Times at which modafinil (200mg) or placebo were administered in double blind fashion are shown as dashed vertical lines (i.e., at 0000hr and 1200hr each day following the first day without sleep).

As in experiment 1, the symptom complaint survey completed at the end of each neurobehavioral test bout in experiment 2 revealed a limited number of adverse experiences associated with modafinil (Table 7). Relative to placebo, subjects receiving modafinil had decreased reports of tiredness (P = 0.003), with a trend for feeling too hot (P = 0.077). All experiences reported were rated low to moderate intensity. Further analysis is continuing on the effects of modafinil on physiological variables (endocrine measures, core body temperature, heart rate) relative to placebo.

Table 7. Experiment 2: Incidence of adverse experience reports during 88h of sleep deprivation for modafinil (400mg/24h) and placebo groups.

	% Subjects reporting		
Adverse Experience	**Modafinil***	**Placebo***	**P value†**
	n = 14	n = 11	
Body			
Headache	50.0	36.4	ns
Ringing in the ears [a]	14.2	9.1	ns
Upset stomach/bowel	28.5	27.3	ns
Itchy skin	50.0	36.4	ns
Back ache/pain	28.5	27.3	ns
Muscle ache/pain	35.7	36.4	ns
Feeling too hot	42.8	9.1	ns
Joint ache/pain	14.2	18.2	ns
Feeling too cold	28.5	45.5	ns
Nervous System			
Tiredness (more than usual)	71.4	100.0	0.003
Difficulty concentrating	92.8	90.9	ns
Difficulty remembering	78.6	81.8	ns
Irritability	50.0	63.6	ns
Feeling confused	21.4	9.1	ns
Excitement (more than usual)	21.4	18.2	ns
Feeling anxious	57.1	36.4	ns
Sadness	21.4	18.2	ns
Dizziness [a]	50.0	45.5	ns

*Percentage of subjects in each condition who indicated they experienced a given symptom during the 30 neurobehavioral testing periods (every 2 hours) for the period from administration of the first pill.

†P values are for the log rank $\chi 2$ used to test the hypothesis that the incidence of adverse experiences differed between subjects randomized to modafinil versus placebo

B. Accomplishments/New Findings at Brigham & Women's Hospital/Harvard:

HARVARD—Project II-a: Data analysis is continuing on the double-blind randomized trial on the effects of modafinil relative to placebo during forced desynchrony. Data acquisition is completed (N = 18). Circadian phase estimates, neurobehavioral performance data, and subjective estimates of sleepiness and mood have been analyzed on all subjects. Neurobehavioral performance data and subjective sleepiness and mood ratings were subjected to non-linear three-factor ANOVA to measure the

effects of treatment condition, hours awake, and circadian hour, as well as, relevant interactions of these three factors. Summarized below, in Figures 2 through 9, are results from analyses of cognitive data including the psychomotor vigilance test (PVT), the Digit Symbol Substitution Test (DSST), the Addition test, the Probed Recall Memory test (PRM), the Trackball test, as well as two measures of alertness (KSS and VAS) and one measure of attentiveness (VAS). Unless otherwise specified raw performance data was used for the N=18 subjects. Data was binned into a total of six circadian hour bins (circadian bins of 60 circadian degrees) and six 'hours awake bins' (each of 4.6 hours in duration). Data are expressed as mean ± SEM. Subjects received modafinil (400 mg/42.8h; split dose: 100mg on awakening, 100mg at 9.58h post awakening, and 200mg 19.16h post awakening) or placebo (on an identical schedule) during the forced desynchrony portion of the study. Figures 3 through 10 display the primary results of the experiment.

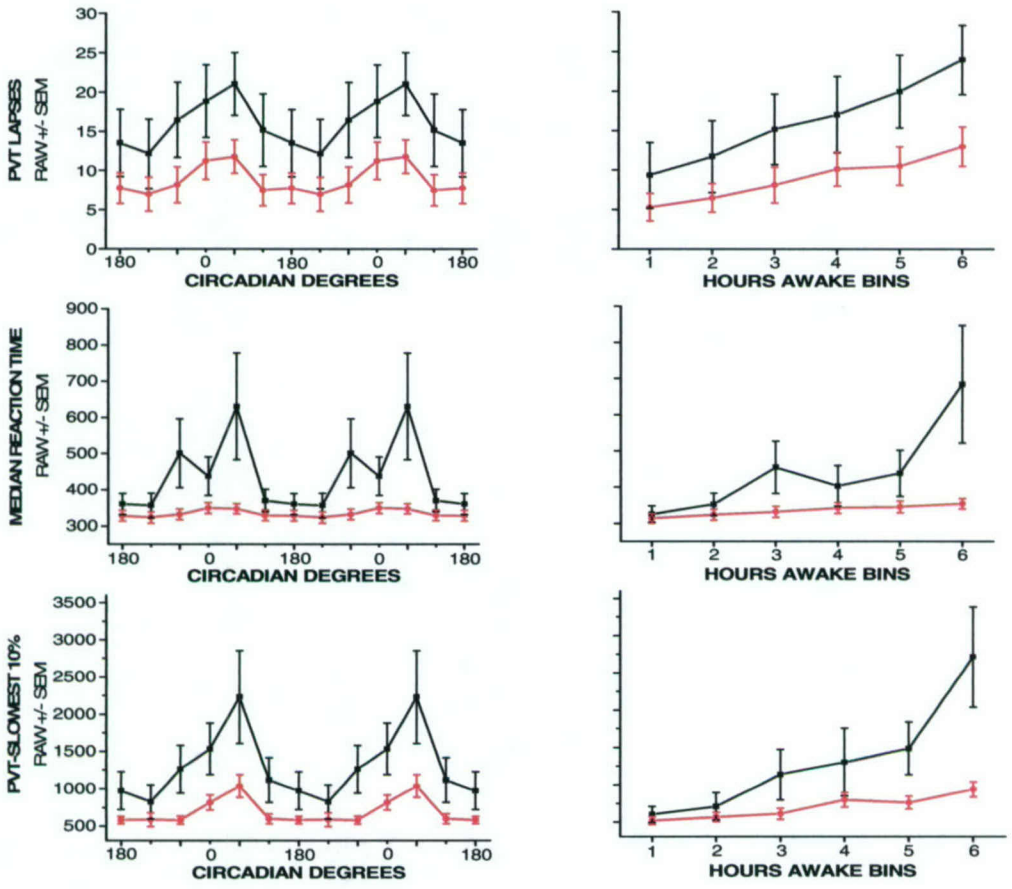

Figure 3. Psychomotor vigilance performance data were binned according to circadian phase (column 1) and across the waking day (column 2). Subjects receiving modafinil are represented by the closed red circles (●). Subjects receiving placebo are represented by the closed black squares (■). Significant main effects for circadian hour and hours awake bins were seen in all parameters ($p < 0.05$). Similarly, all three PVT measures showed significant interactions of hours awake by condition ($p < 0.05$). Significant interactions for circadian hour by condition were also seen for lapses and median reaction time with significant 3-way interactions for median reaction time and slowest 10% responses (all $p < 0.05$).

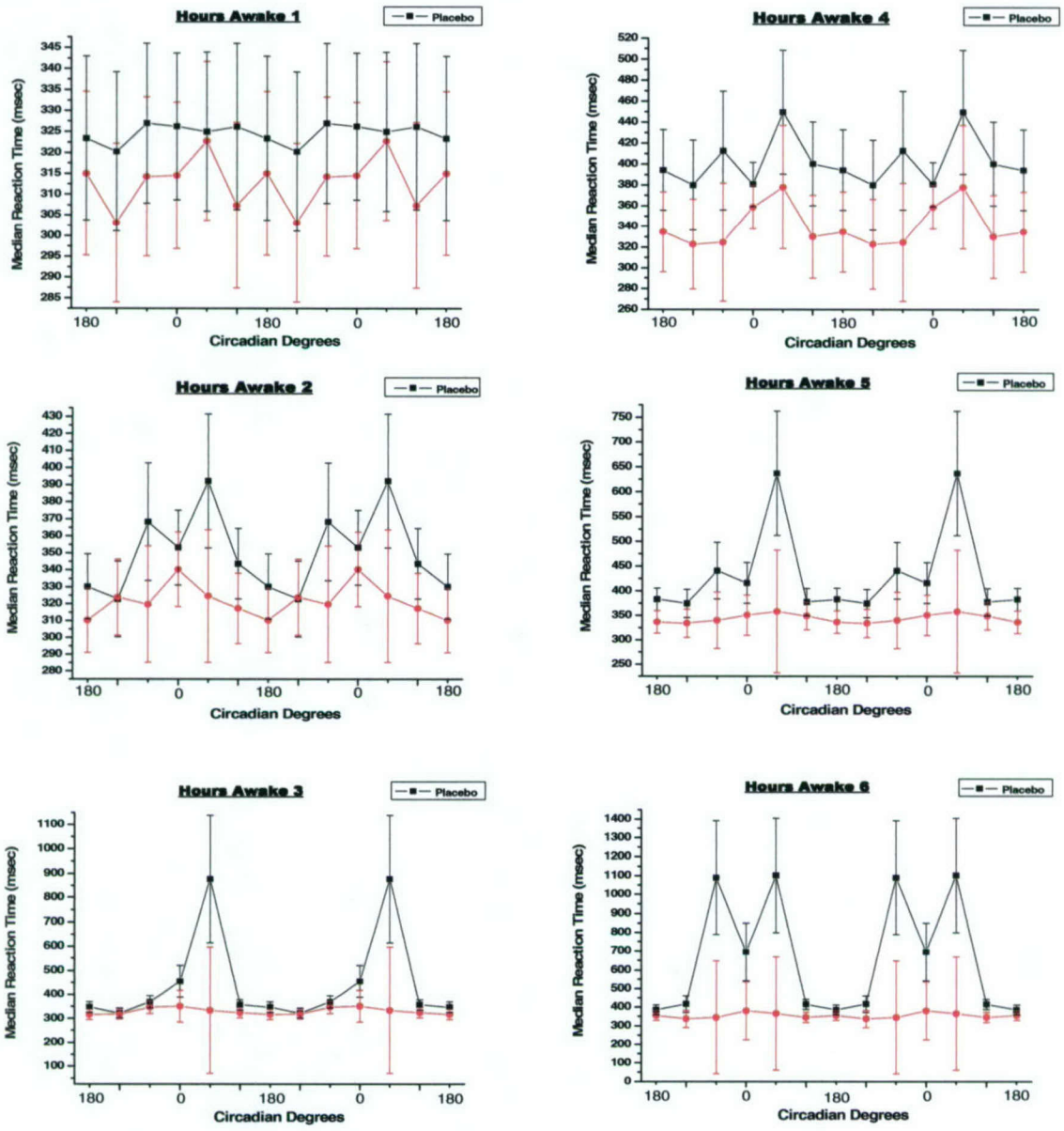

Figure 4. The median reaction time, graphed as a function of circadian phase for each hour of wakefulness, demonstrates that PVT median reaction times varied according to both the circadian hour and cumulative number of hours awake in an interactive fashion (significant 3-way interaction of condition x hours awake x circadian time, $p < 0.05$). As expected, as the time awake increased (i.e. increasing homeostatic pressure) the amplitude of the circadian variation in performance tended to increase in the placebo group. In contrast, in the modafinil group performance remained relatively stable across all circadian phases, with decreased amplitude in the circadian rhythm of reaction time performance—this is particularly evident at 5 and 6 hours of wakefulness. For all durations of prior wakefulness, the median reaction time was faster in those subjects receiving modafinil relative to those receiving placebo. Modafinil group (●); placebo group (■).

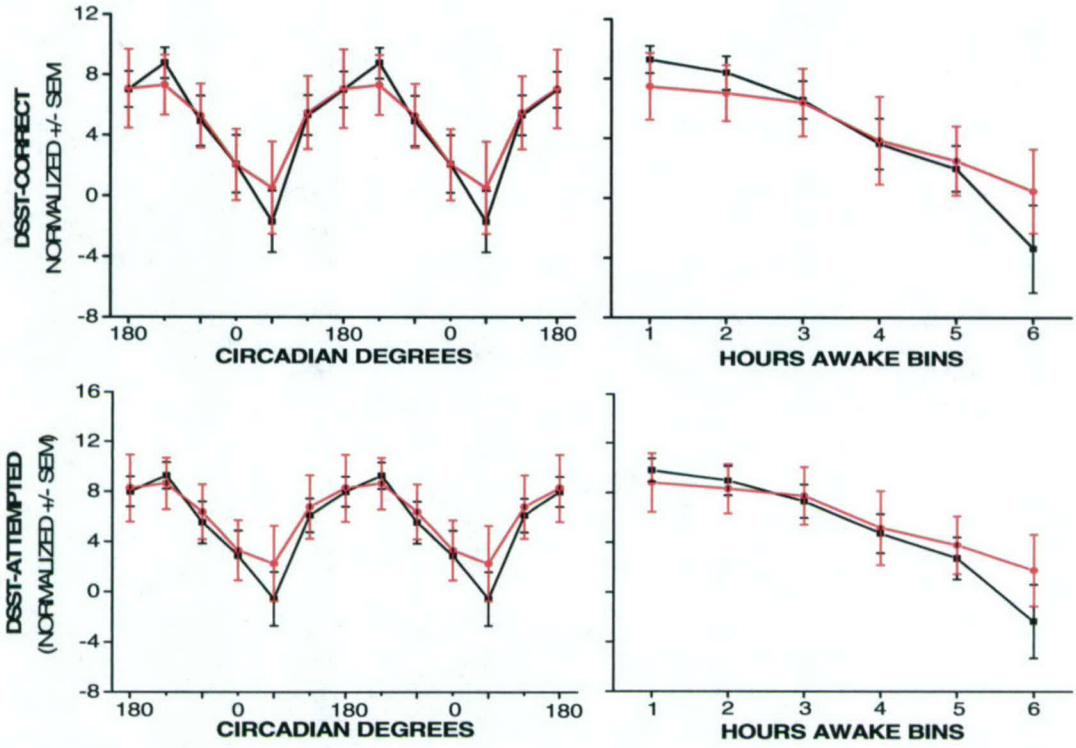

Figure 5. Baseline day 3 results on the Digit Symbol Substitution Test (DSST) differed between conditions. To account for this baseline differential DSST data was normalized (subtracting baseline day 3 performance data from all data points). As expected a robust circadian and hours awake effect on performance was seen. Also a significant interaction of hours awake by condition was also observed ($p<0.05$). All other comparisons were statistically non-significant. Modafinil group (●); placebo group (■).

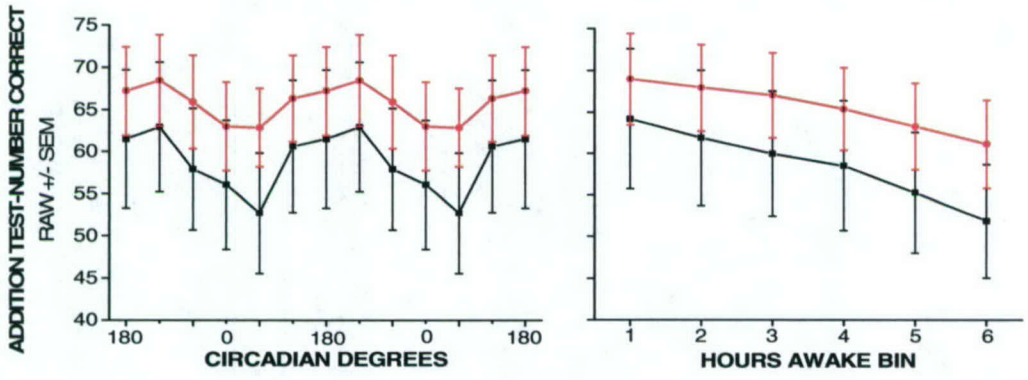

Figure 6. Cognitive throughput as measured by the Addition test demonstrated significant hours awake, circadian, and circadian by condition effects (all $p < 0.05$)

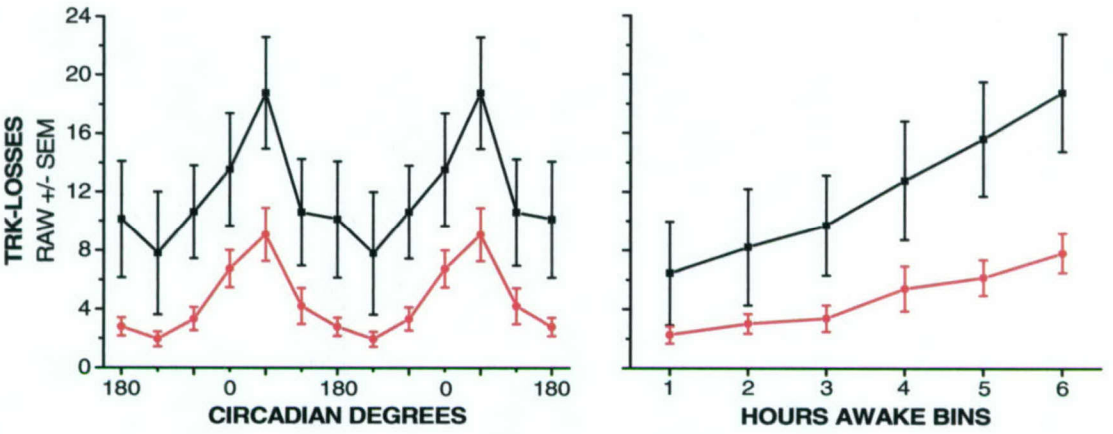

Figure 7. Trackball control losses were reduced by modafinil. Specifically, a trend to a main effect by condition was noted ($p = 0.076$) as well as a significant interaction of condition by hours awake ($p < 0.05$). Main effects for circadian hour and hours awake were also seen. Modafinil group (●); placebo group (■).

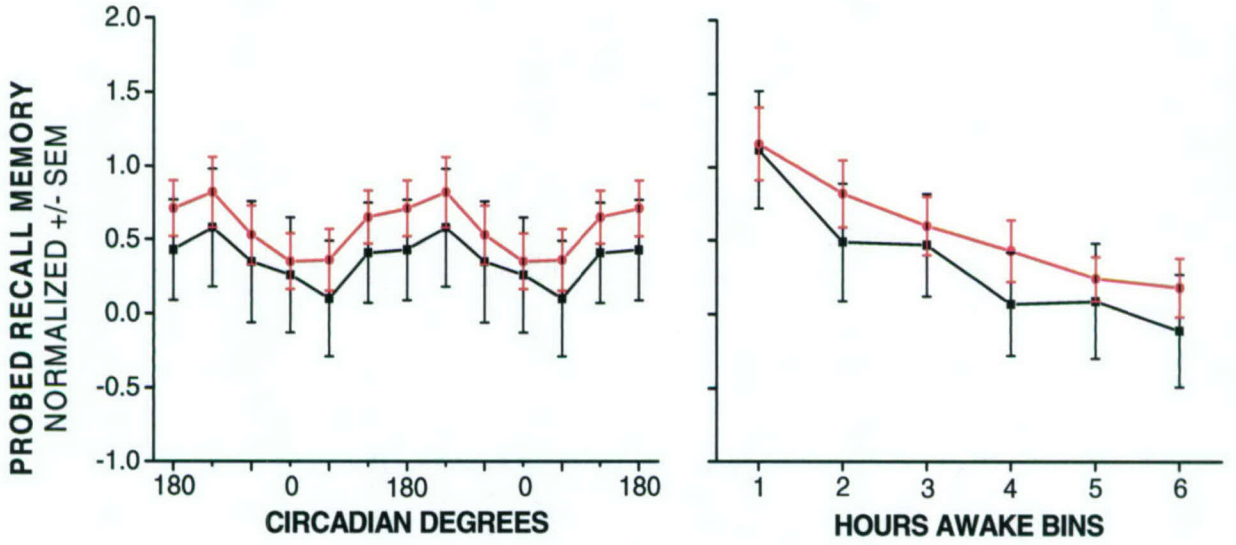

Figure 8. As baseline day 3 performance on the Probed Recall Memory (PRM) task also varied between the two treatment groups, data were normalized for the PRM. Though robust effects of circadian hour and hours awake were demonstrated, no significant effect of condition was noted.

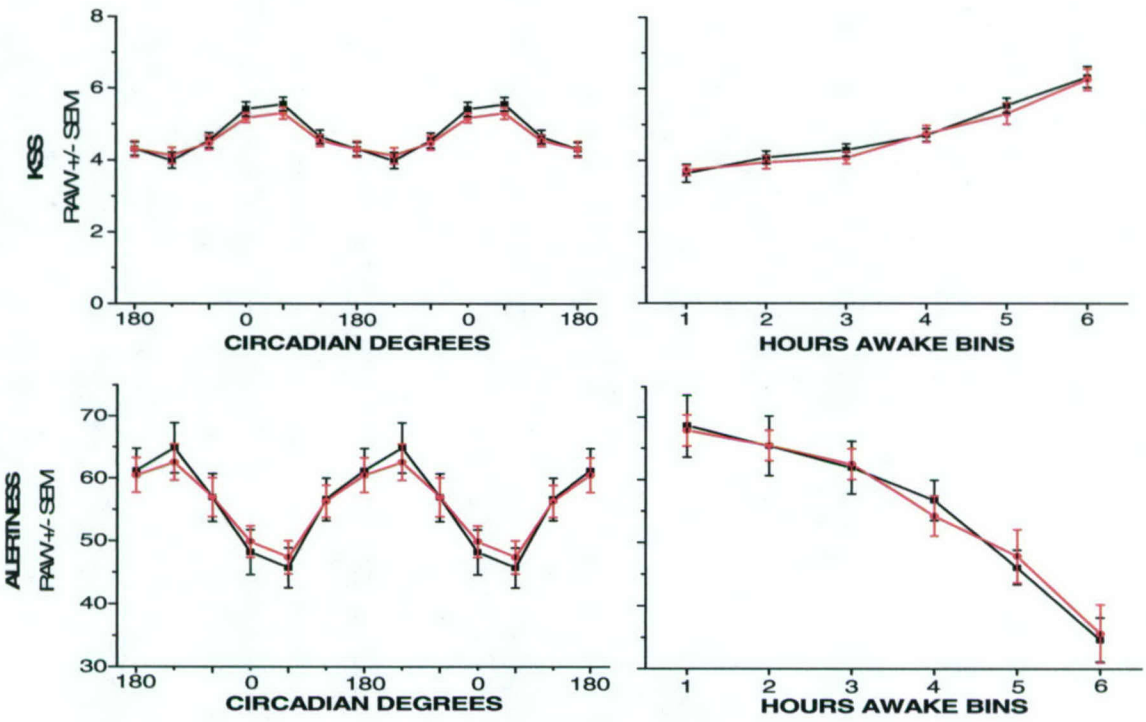

Figure 9. Two measures of alertness were tested. These were the Karolinska Sleepiness Scale and the Visual Analog Scale (sleepy-alert). As elsewhere, robust main effects for circadian and hours awake were observed ($p < 0.05$) but there was no treatment effect. Modafinil group (●); placebo group (■).

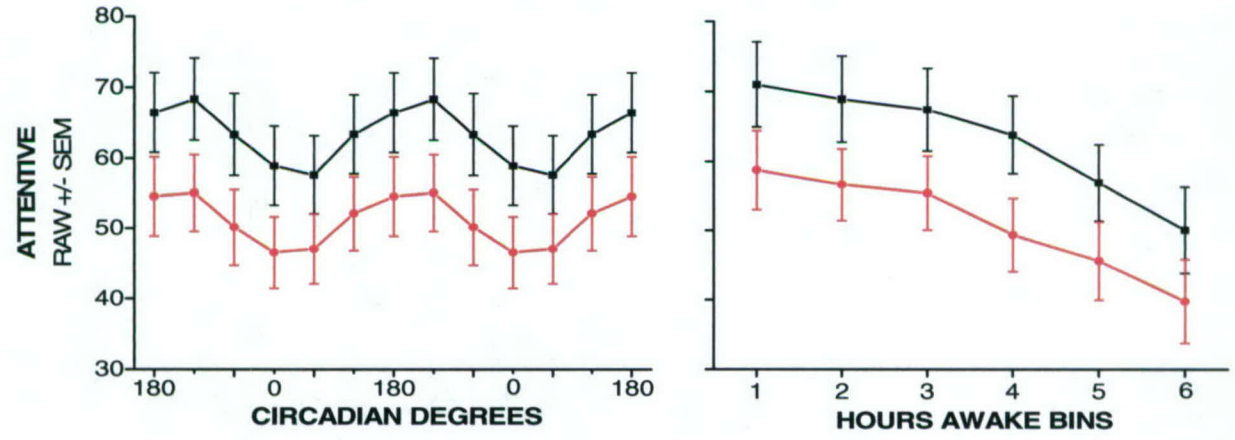

Figure 10. VAS testing using the anchors Dreamy-Attentive (0-100 scale) demonstrated significant main effects for circadian hour and hours awake as expected. A significant three way interaction was also observed ($p < 0.05$). Specifically, the modafinil group reported reduced attentiveness by this measure.

In summary, analysis of cognitive data thus far has demonstrated that modafinil is an effective countermeasure to the performance degradation associated with work at both adverse circadian phases and during prolonged wakefulness up to 28 hours. This is the first specific demonstration of modafinil's efficacy in offsetting the deleterious effects of operating at an adverse circadian phase on neurobehavioral performance parameters. Additionally, these data indicate that modafinil's efficacy as a countermeasure is maintained in a laboratory-based scenario analogous to that of recurrent redeployments, commonly experienced by members of the armed forces. Alertness was not affected by treatment condition but subjectively reduced attentiveness was noted in subjects in the active treatment group.

HARVARD—Project II-b: We released a new version of the *Circadian Performance Simulation Software* (CPSS 1.2, © Brigham and Women's Hospital, August 2002). In this version, we have responded to users' suggestions by enhancing both the simulation input features and the graphical output of the simulation results. We also made two important changes to the mathematical models contained within CPSS.

Interface Changes: In order to improve the user experience when inputting simulation protocols, the routines used to check for valid user input in CPSS version 1.0 have been replaced with more thorough and enhanced versions. In addition, CPSS version 1.2 now creates graphs of the sleep/wake and light protocols in the protocol dialogue box whenever protocol files are saved. These graphs allow the user to check their entered protocols prior to simulating them. All the graphs within CPSS 1.2, including the simulation output graphs, have been updated to allow the user to change graphing properties, including axis' scales. The event creation function has been modified to allow for real-valued intensities to be entered rather than integers only (as was the case in CPSS version 1.0). Lastly, in CPSS 1.2 the allowable protocol length has been increased so that much longer protocols may now be simulated.

Model Changes: In the part of CPSS 1.2 in which we predict circadian phase on the basis of light exposure, we have refined our definition of circadian phase so that it is more stable across all circadian amplitudes. In the part of CPSS 1.2 in which we predict the homeostatic (wake-dependent) rate of decay of alertness and performance, we have revised the model so that the rate is dependent upon the level of the homeostat rather than the time since waking. This revised definition allows the model to better-fit experimental data.

CPSS can be found at http://dsm.bwh.harvard.edu/bmu/cpss/

For the addition of the effects of caffeine on neurobehavioral performance and alertness, we fit functions to the data. For all subjective and objective measures except ADD, a 2-time-constant exponential was the best fit to the homeostatic component of neurobehavioral performance; the ADD measure was best fit by a Gaussian. The data from the caffeine group could fit by the same functions as the data from the placebo group. There were differences in the mean and amplitude of fits between groups. Data

from the caffeine group had longer time constants of the homeostatic fit for the objective but not subjective measures.

The best-fit of the amplitude of the 24-hour component of the circadian rhythms in each subjective and objective measure was a single-time constant exponential fit, although the time constant was close to zero, resulting in a near-linear curve. For subjective measures, there was no difference in relative amplitude between caffeine and placebo groups across homeostatic bins. For objective measures (ADD, DSST, PVT) the circadian amplitude was smaller across all homeostatic bins for the caffeine group.

In conclusion, the fits to data from caffeine and placebo groups are different. Caffeine lowered the amplitude of the fit function of subjective measures of alertness. However, caffeine affects components of objective neurobehavioral performance reducing the amplitude of the circadian component of the function. The lack of correlation between subjective and objective measures of alertness is similar to that seen in non-pharmacological studies. These descriptive mathematical models are a productive step in constructing interactive models for predicting the effect of caffeine on performance during a variety of sleep-wake schedules.

We added a non-photic component to the model. While our current mathematical representation of the human circadian pacemaker has proven useful in many experimental situations, it uses as input only a direct effect of light on the circadian pacemaker. Although light has been shown to be the primary synchronizer of the circadian pacemaker across a number of species, studies in both animals and humans have confirmed the existence of non-photic effects that also contribute to phase shifting and entrainment. We modified our light-based circadian mathematical model to reflect evidence from these studies that the sleep-wake cycle and/or associated behaviors have a non-photic effect on the circadian pacemaker. In our representation, the sleep-wake cycle is a non-photic drive on the pacemaker that acts both independently and concomitantly with light. Further experiments are required to validate fully our model and to understand the exact effect of the sleep-wake cycle as a non-photic stimulus for the human circadian pacemaker .The revised model is significantly improved at predicting circadian phase (and by inference performance and alertness since they are strongly affected by circadian phase) under dim lighting conditions, including when bedrest occurs at adverse circadian phases. The manuscript describing this work has been submitted for publication.

C. <u>Accomplishments/New Findings at Hypnion:</u>

A major goal of the PRET Center was to partner academic and private industry in a synergistic effort to find new ways to counter the adverse effects of sleep deprivation. The third research program of this Center has involved preclinical basic research and development in a commercial setting that was born out of this AFOSR-PRET program. Hypnion, Inc. was co-founded by Dr. Dale Edgar in March of 2000 as a means to transition his basic research and technological innovations at Stanford University to commercial viability and production. SCORE-2000™, a preclinical sleep-wake drug discovery and evaluation technology invented under the auspices of the AFOSR-PRET

from 1999-2000 became Hypnion's founding platform technology. Using this technology, Dr. Edgar and his colleagues at Hypnion have dramatically accelerated and advanced novel sleep-wake therapeutic drug discovery. Hypnion has advanced a novel drug program for insomnia from preclinical concept to Phase-IIa clinical trials. Hypnion has also performed a broad array of basic research into novel wake-promoting therapeutics, complementing and expanding upon the research initiatives of this AFOSR-PRET Center. As in previous years, this component of the AFOSR-PRET Center has been vital to the continued identification and development of "next-generation" optimal pharmacological countermeasures to performance-impairing sleepiness and related performance impairment in Air Force operations.

Founding of Hypnion, Inc. In March of 2000, Drs. Dale Edgar, Emmanuel Mignot, Michael Rosbash, Joseph Takahashi and Karen Moore founded the first biotechnology company dedicated exclusively to the challenges of sleep-wake drug discovery—Hypnion, Inc. In September of 2000 the company's core Executive personnel were assembled and Series-A venture financing of $10.4MM was secured. The founding technology transfer commenced in August of 2000 with the licensing of SCORE-2000™ from Dr. Edgar via Stanford University. The actual physical technology transition began in October of 2000, with the leasing of a suitable building for Hypnion's research initiatives in Worcester, MA. As the principle scientific founder, Dr. Edgar took an approved 2-year leave of absence from his faculty post at Stanford University in California, moved to Massachusetts, and personally enable the transition and scale-up of the science and technology developed in his Stanford University Laboratory. This included, too, the transition of his AFOSR-PRET sponsored research and technology, as well as his current AFOSR-PRET Center sponsored research activities. During his leave of absence from Stanford, Dr. Edgar simultaneously managed his ongoing laboratory research program at Stanford, and established the research programs at Hypnion, setting the company on its current path. In the Fall of 2002, Dr. Edgar joined Hypnion permanently, and presently serves as the Company's Chief Science and Technology Officer. Despite the very difficult financial environment caused by Enron, Worldcom, 9/11, and other unfortunate events in 2001-2002, Hypnion has been very successful and is considered the leader in sleep-wake therapeutic discovery and innovation. Within the first 3 years of operation, Hypnion raised over $60 million from some of the most prestigious and rigorous venture capital firms, including MPM Capital, Forward Ventures, Advanced Technology Ventures, Oxford Biosciences, Flagship Ventures, GIMV, and others. In 2003 the company was named one of the most influential biotechnology companies in the World by Accumen Journal. The company presently employs approximately 50 people. Hypnion constitutes a bona fide AFOSR transition in that the founding scientist, Dr. Edgar, the founding platform technology (SCORE-2000™), and the Company's scientific agenda were successfully transitioned from an AFOSR-PRET sponsored academic research setting into industry.

Transition and Scale-Up of SCORE-2000™ at Hypnion. Hypnion's founding platform technology, SCORE-2000™ was first designed and prototyped under the auspices of the AFOSR-PRET Center (F49620-95-1-0388), with additional funding support for equipment acquisition from an AFOSR-sponsored DURIP grant to Dr. Edgar. The

practical mechanics of transitioning this complex technology occurred in the Fall of 2000. Hypnion has applied approximately $5 million toward the transition scale-up and improvements in the SCORE-2000™ software and hardware. This investment has enabled Hypnion to comprehensively monitor the physiology and behavior (sleep architecture, wake, motor tone, locomotor activity, body temperature, feeding, drinking and heart rate) continuously, simultaneously and in real-time from up to 320 animals. The large scale and complexity of this initiative is unprecedented in the sleep and pharmaceutical research communities. The large-scale deployment of SCORE-2000™ at Hypnion has enabled for the first time, a cost-effective and high-volume method of establishing in vivo sleep-wake structure-activity relationships (SAR) that have enabled medicinal chemists to optimize compounds for clinically-relevant physiological endpoints early in the preclinical discovery process (see Figure 11).

To manage, validate, analyze and assure the lasting integrity of the high volume of data collected, Dr. Edgar assembled a team of information scientists, and recruited his long-time colleague, Wesley Seidel, from Stanford to help coordinate this team's efforts. They in turn, created sophisticated data quality assurance technology (SCOREView™ and ReSCORE™) and integrated it into an Oracle-9 database (HypNET™) that provides access to all of the data for data mining and pharmacological signature profiling. The later enabled objective preclinical assessment of Hypnion's novel chemical entities (NCEs) for lead optimization and quantitative comparison with pharmacological standards. At present there are approximately 70 pharmacological standards in the database, representing the receptors and transporters of almost every major pharmacological class. These pharmacological standards have been analyzed retrospectively, and in some cases, prospectively, for concordance with their known clinical effects and certain key side effects. The concordance agreement is in excess of 90%, making SCORE-2000™ one of the most predictive preclinical CNS drug discovery assay systems ever created.

Hypnion has successfully used SCORE-2000™ in three fundamental ways.

(i) Identification and characterization of compounds designed to increase sleep consolidation and sleep maintenance, and to shorten the latency to return to sleep. The primary therapeutic indications include the treatment sleep maintenance insomnia (28 million US patient population) and sleep disturbance prevalent during day-time sleep in night-shift workers and military night operations. Hypnion's drug discovery initiative may also have applications in battlefield sleep disturbance and post-traumatic stress. Critical to Hypnion's efforts has been the identification of a novel compound series that can shorten the latency to return to sleep and enhance sleep maintenance without also causing myorelaxation, REM inhibition, cognitive malaise, or negatively impacting the normal and natural reversibility of the sleeping state (e.g., awakening and responding appropriately to get out of harms way). Although not part of the F49620-00-1-0266 research agenda or specific aims, Hypnion's insomnia discovery program has identified multiple clinical candidates that meet these stringent requirements. The lead in this series has completed Phase-I and is presently entering Phase-IIa clinical trials.

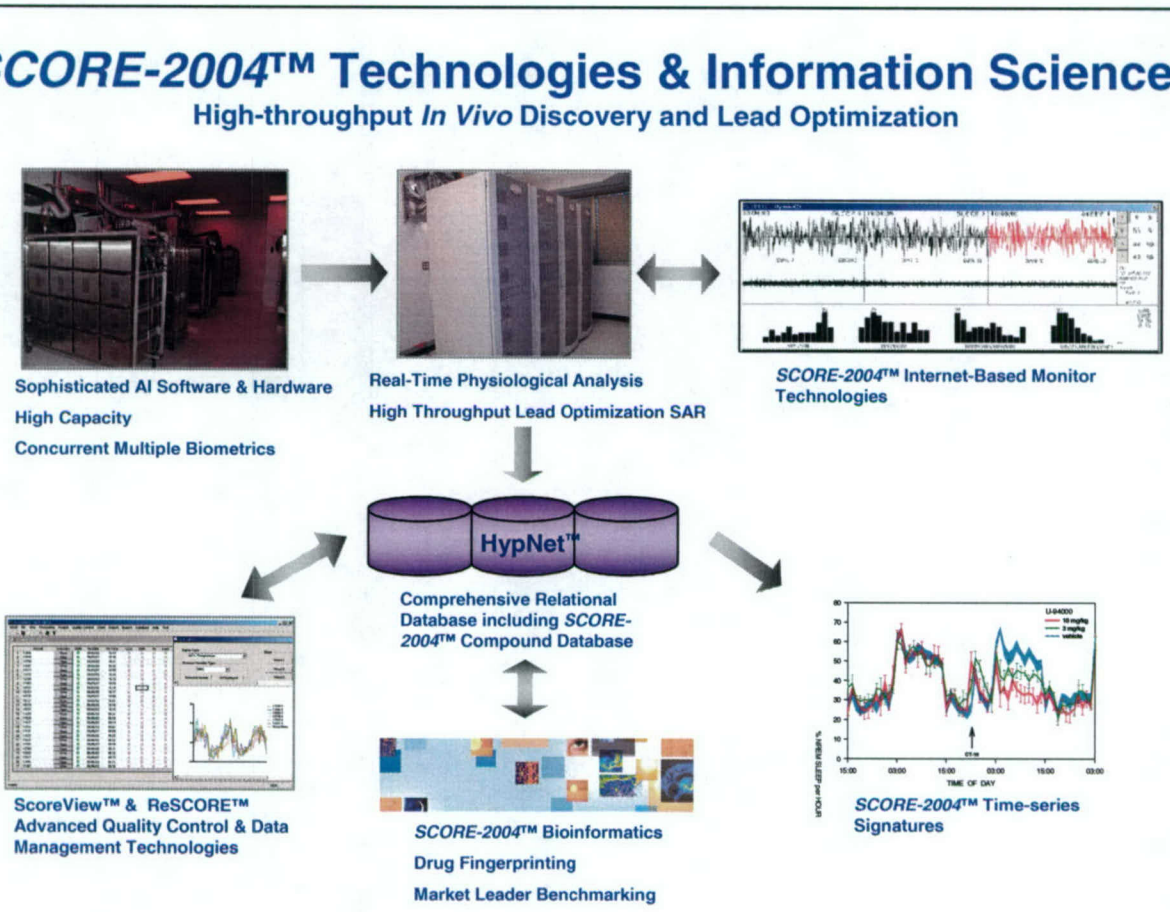

Figure 11. Components of the recently revised and expanded SCORE-2000™ drug discovery and evaluation system include an environmentally-controlled home-cage study environment, an array of servers, real-time portals accessible with proprietary Windows-based SCORE-Monitor software, extensive quality control and data analysis software (SCOREView™ and ReSCORE™ bridged to SAS statistical analysis software) and a Oracle-9 relational database that houses all information about the chemistry, pharmacology and toxicology of compounds.

(ii) Identification and characterization of compound classes that are best suited to promote and maintain wakefulness without imposing incremental increase in accumulated physiological sleepiness and devoid of the unwanted side effects common to psychomotor stimulants (euphoria, dependence, hyperactivity, rebound hypersomnolence).

(iii) Performance of preclinical basic and applied research into the properties and mechanisms of wake-promoting pharmacological agents, with emphasis on their interaction with CNS mechanisms responsible for compensatory hypersomnolence after sustained wakefulness. This is the main preclinical research activity that has been sponsored, in part, by F49620-00-1-0266.

Rationale for WPT discovery strategy. Hypnion's strategic search for novel and functionally selective wakefulness-promoting therapeutics derives from past work by this AFOSR-PRET Center and The Opponent Process Model of Sleep-Wake Regulation developed by Dr, Edgar (Figure 12). The model, derived from primate data (squirrel monkey and human), posits that physiological sleepiness is the product of two opponent physiological controllers. One is an active mechanism that promotes and maintains wakefulness initiated by the suprachiasmatic nucleus (SCN). In primates and rodents, the SCN is required for active-phase wakefulness consolidation. The other process is homeostatic in nature and increases sleepiness in opposition to the CN-dependent alertness generated by the SCN. The more the SCN consolidates wakefulness, the greater the prior wake duration, and in turn, the greater the homeostatic sleep drive. Normally the SCN-dependent alerting signal exceeds homeostatic sleep drive during the day, permitting wakefulness consolidation. In primates, this alerting signal is greatest in the hours preceding habitual "bed time." The strong SCN-dependent alerting

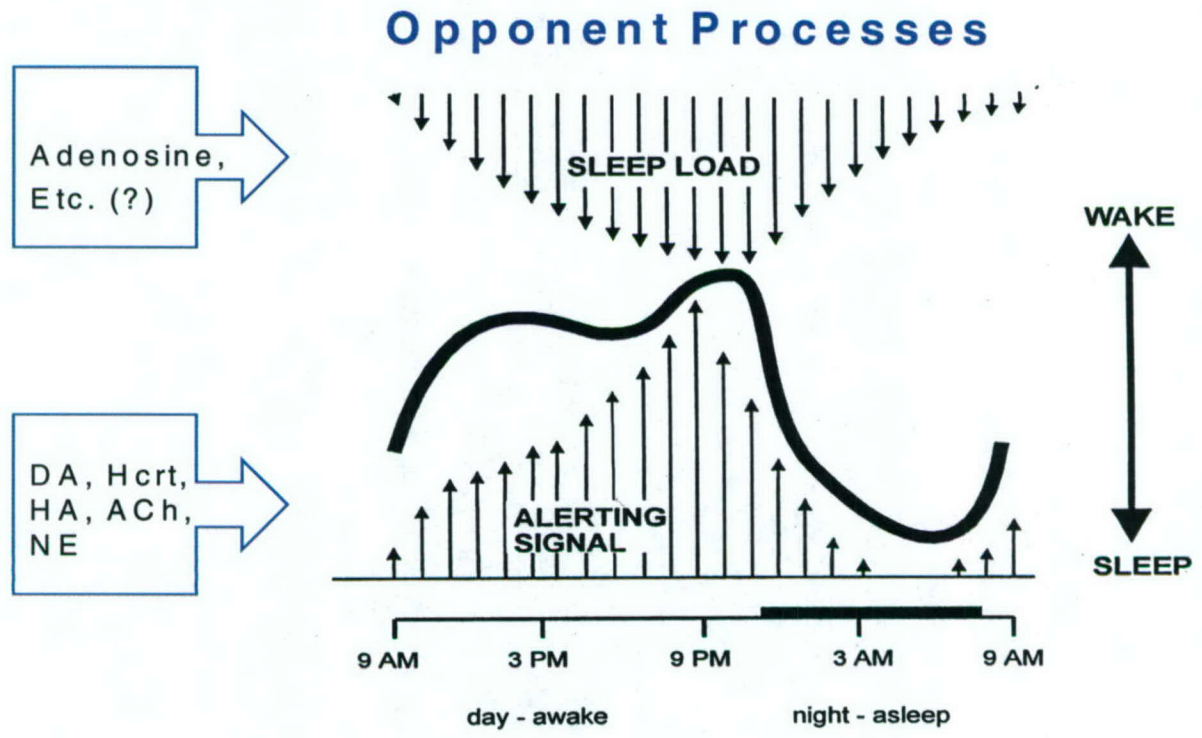

Figure 12. Opponent Process Model of Sleep-Wake regulation (Edgar et al. 1990, 1993).

signal is the principle cause of sleep disturbance in night-shift workers (who try to sleep during day-time hours) and during jet-lag. In each case sleep quality is impaired by the strong physiological wakefulness drive originating in the central nervous system (CNS) and temporally orchestrated by the SCN.

The neurobiological underpinnings of these opponent processes are only partially understood, and have been further elucidated as part of this AFOSR-PRET Center research. The SCN-dependent alerting neurobiological pathway has become better understood with the recent discovery of orexin/hypocretin abnormalities in narcoleptics by Emmanuel Mignot at Stanford University. Dantz, Edgar and Dement had previously demonstrated that narcoleptic lack normal SCN-dependent alerting, manifest by inability to consolidate wakefulness in a human 90-minute day protocol. Mignot et al., at Stanford, and Yanagasawa et al., at UT Southwestern demonstrated that narcolepsy involve a disorder of orexin/hypocretin neurotransmission and that this transmitter system is a functional relay between the SCN and the major mechanisms involved in cortical arousal, behavioral arousal, and attentional arousal. As part of the AFOSR Center research, Edgar and Mignot found that small ICV microinjections of orexin/hypocretin produced profound and sustained wakefulness comparable to the effects of the potent dopaminergic stimulants. Other studies by Mignot and others further revealed that histamine neurons in the tuberomammilarry region of the posterior hypothalamus, the noradrenergic neuron containing locus coeruleus receive major input from orexin/hypocretin neurons and are the principal down-stream effectors of the SCN-dependent alerting mechanism. Wakefulness, attention and memory depend heavily on histamine neurotransmission which positively and reciprocally reinforces cortical and behavioral arousal mediated by ascending cholinergic, noradrenergic, glutamatergic and dopaminergic systems. Thus, any one of these transmitter systems is, in theory, a pharmacological target for enhancing wakefulness and attention. As will be discussed further below, Hypnion's AFOSR-PRET Center contributions include a systematic assessment of the therapeutic viability of these targets "SCN-dependent alerting targets."

Opposing SCN-dependent alerting is the homeostatic drive to sleep. The more prolonged the waking duration, the greater the homeostatic sleep drive. The physiological and operational properties of this sleep drive have been well documented in many studies over the last 2 decades, including notably, the research by the AFOSR-PRET Center principal investigators. The neurobiological basis for homeostatic sleep drive is very poorly understood. In the late 1990's the most prevalent opinion within the sleep research community was that adenosine mediated homeostatic sleep drive. This is not to say that there are not other endogenous sleep promoting molecules in the CNS. Rather, the largest body of evidence collected to date pointed to the inhibitory action of adenosine through the A1 adenosine receptor. If in fact the A1 receptor is the principal mediator of homeostatic sleep drive, then high affinity, brain penetrant and selective adenosine A1 antagonists should be "most" effective in promoting wakefulness in sleep-deprived subjects. As part of this AFOSR-PRET Center program, this hypothesis was directly tested by applying parametric sleep deprivation in animals and then testing multiple doses of wake-promoting compounds across multiple pharmacological classes, including a novel class of potent non-xanthine adenosine receptor antagonists.

Finally, if the level of sleepiness-alertness is mediated by multiple neurotransmitter systems, it should be possible to identify synergistic combinations of wakefulness-

promoting therapeutics (WPT) that activate the SCN-dependent alerting cascade and inhibit the homeostatic drive toward sleep, based upon the principles described above. This hypothesis was tested in detail as part of this AFOSR-PRET Center research program.

Compensatory sleep profiles of candidate WPTs. One of the most significant physiological discoveries to emerge from the preclinical efforts of this AFOSR-PRET Center addresses the homeostatic consequences of pharmacology-induced wakefulness. Several dozen compounds have now been thoroughly studied in this context. When compounds are tested for their wake promoting efficacy, and dose response curves established, equipotent pharmacodynamics doses can be identified by the quantitative displacement of NREM sleep. For statistically equipotent doses, compounds differentiate with regard to side effects. The most salient of these side effects are hyperactivity, rebound hypersomnolence and the cumulative compensatory sleep response (CSR).

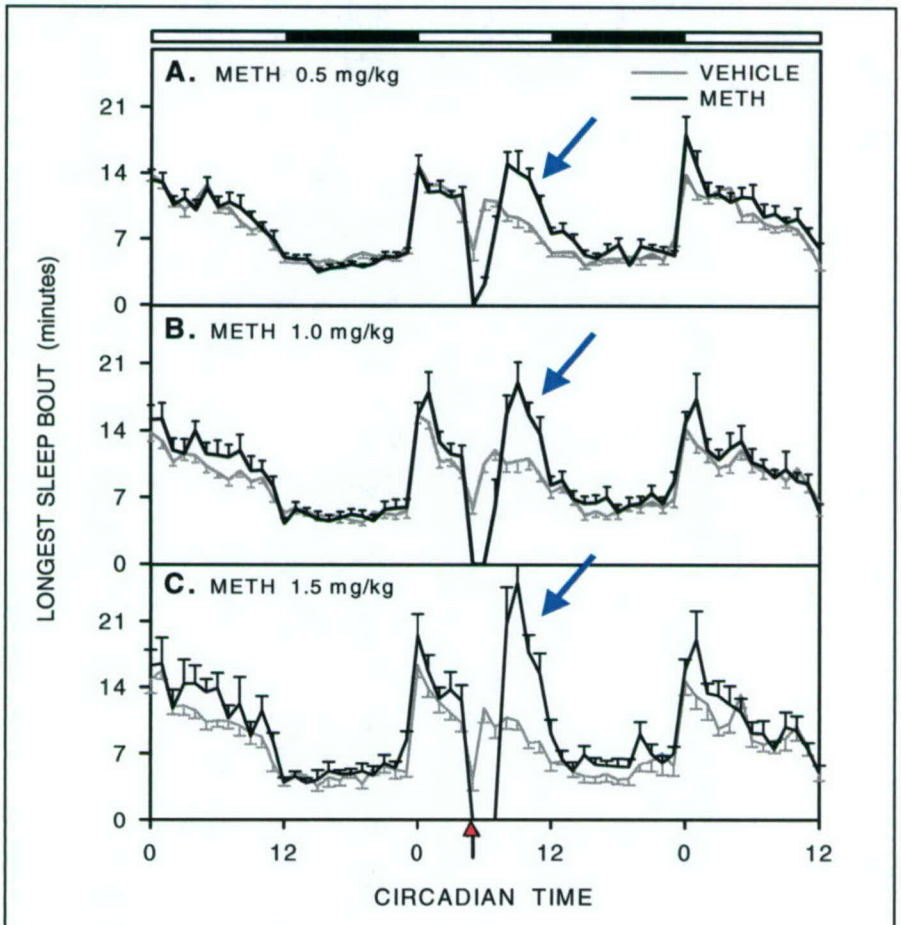

Figure 13. Dose proportional increase in rebound hypersomnolence (arrows) after methamphetamine-induced wakefulness (0.5, 1.0 and 1.5 mg/kg). CSR metric is longest sleep bout, which is directly proportional to physiological sleepiness in the rat.

Our expanded studies of amphetamines revealed, for example, that the acute hypersomnolence that follows drug-induced wakefulness is dose proportional, increasing in severity in a lawful pharmacological manner that also parallels the wake-promoting efficacy and is linear on a dose log-plot. Figure 13 shows these dose-dependent responses to three doses of methamphetamine.

A sort order of equipotent wake-promoting compounds tested in SCORE-2000™ has revealed a consistent theme, illustrated in Figure 14. Across the range of known, potent, wake promoting agents, dopamine transporter inhibitors (DAT inhibitors) and dopamine-norepinephrine transporter inhibitors (DNRIs) invoke the smallest amount of acute rebound hypersomnolence and total CSR, as compared to every other known wake-promoting pharmacological class. Ranked second are the adenosine A1 and mixed A1/A2 receptor antagonists which were thoroughly studied and differentiated from caffeine and are discussed in detail, below.

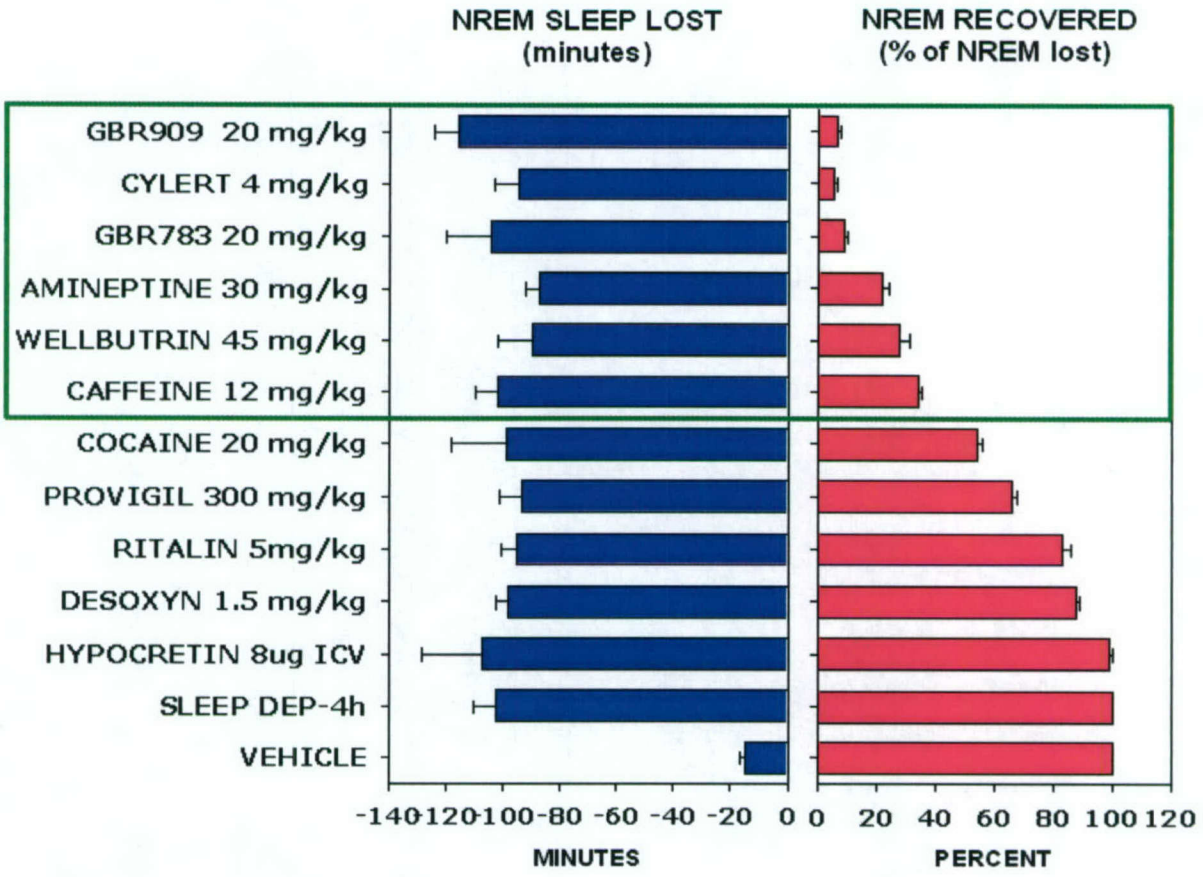

Figure 14. Compensatory sleep response (NREM recovered; red) following pharmacodynamically equipotent wake promoting doses of stimulants administered at CT-5.

Histamine H3 autoreceptor antagonists. As mentioned above, the excitatory monoamine transmitter histamine is a critical transmitter necessary for SCN-dependent alerting and the normal consolidation of day-time wakefulness. In the brain, the effects of histamine are primarily mediated through H1 receptors, which exist as 7TM homodimers, and are remarkably conserved across species. Indeed, bovine, rat and human H1 binding affinities (Ki) for antihistaminergic ligands are remarkably similar. Vesicular release of histamine from histamine neurons is governed in part by an autoregularory loop mediated by H3 receptors. Histamine in the synaptic cleft normally inhibits histamine release through the H3 autoreceptor. Therapeutically, one may postulate that increased CNS histamine neurotransmission would increase wakefulness, attention and cognition, based upon a wealth of indirect data in the literature. The story as gleaned from the literature is not straightforward, however, due to the interspecific properties of the H3 receptor itself. Like the H1 receptor, the functional H3 receptor exists as a dimmer. But in contrast to H1, the H3 receptor forms a wide variety of heterodimers and oligodimers, hybridizing H3 active site subunits with H2 and H4 receptor sub-units, and with subunits from other monoamine transmission systems. Further, there is genetic variation in the sequence of the H3 subunits, with significant functional differences between human and rat. Thus, there are H3 ligands that may work well in rat but are inactive in human, and visa versa. The most recent discovery efforts in H3 have attempted to identify NCE with good affinity for both rat and human H3; a strategy that greatly facilitates preclinical development success. Hypnion has examined the wake promoting potential of multiple H3 antagonists using the SCORE-2000™ assay. To foster this effort. We have consulted two of the World's foremost experts on H3 chemistry: Dr. Henk Timmerman and Dr. Rob Leurs, who are professors of medicinal chemistry at the Vrije University of Amsterdam in The Netherlands. We have also collaborated with Dr. Clark Tedford to evaluate the wake-promoting potential of non-thiourea based H3 antagonists that were developed by Gliatech, Inc. Finally, we examined the wake promoting potential of ciproxifan, an H3 antagonist developed by INSERM (France) and reported to have potent wake-promoting activity in cats (Figure 15).

The basis of this effort began with the assessment of the thiourea H3 antagonist thioperamide in rats using SCORE-2000™. Thiourea-based ligands are contraindicated for clinical development because of hepatotoxicity with chronic dosing, but it nonetheless provides a wake-promoting efficacy benchmark. Thioperamide has low nanomolar affinity for H3 and is highly brain penetrant. At 4 mg/kg, thioperamide almost tripled the average wake-bout length per hour in rats (duration of time an animal spontaneously remains awake; veh=10.2 ± 2.1 vs thioperamide 27.1 ± 7.3, P=0.05), with a duration of action lasting about 4 hours. Interestingly, total wake time increase was not impressive at any time post-treatment (70% below nominal expectation, defined by effects reaching or exceeding circadian wake levels during the circadian activity phase (lights-off). At this dose, brain levels are reported to exceed the Ki by more than 10x, so higher doses were not tested. Gliatech H3 antagonists differ from thioperamide in that they are based on a non-thiourea chemical scaffold, but are otherwise sterically and electronically similar. The Gliatech compounds are also noteworthy as they have shown positive results in preclinical models of cognition. GT2016 (10 and 30 mg/kg),

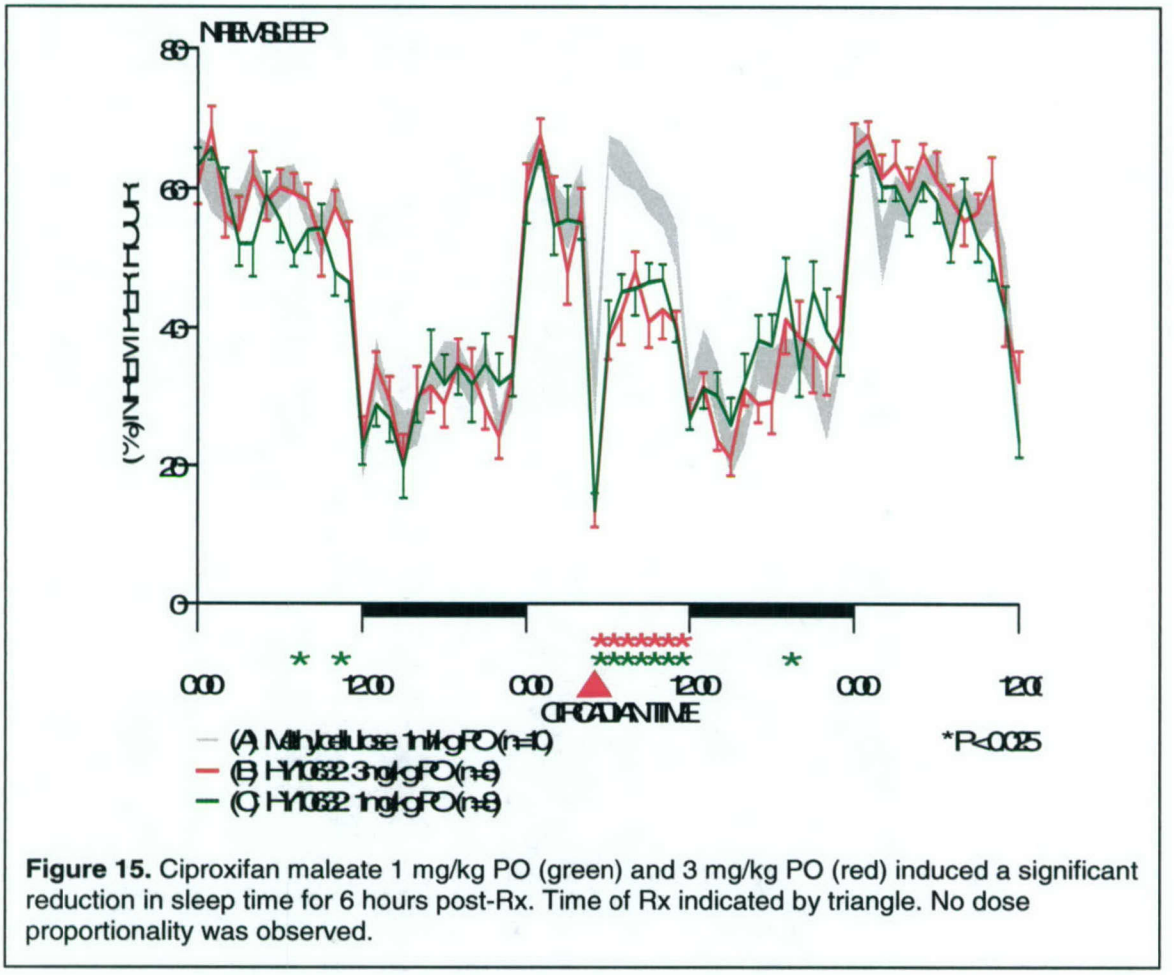

Figure 15. Ciproxifan maleate 1 mg/kg PO (green) and 3 mg/kg PO (red) induced a significant reduction in sleep time for 6 hours post-Rx. Time of Rx indicated by triangle. No dose proportionality was observed.

GT2227 (3, 10, 15, and 20 mg/kg), GT2331 (1 and 3 mg/kg) were tested. All three of these compounds showed weak effects on total wake time as compared to wake-promoting benchmark standards like modafinil, caffeine, or psychostimulants (d-amphetamine). In the case of GT2227, the compound showed an unambiguous inverted-U dose response curve, with peak waking efficacy at 10 mg/kg. These findings were discouraging, and became complicated further by the late discovery by Gliatech that their compounds, which were all optimized for rat H3, had very poor affinity for the human H3 receptor. Despite Gliatech's preclinical faux pas, there remains considerable interest in H3 ligands for cognition in large pharmaceutical companies. Given this, and based on recent cat studies by Lin and colleagues in Lyon, which suggest potent efficacy of ciproxifan (a low nanomolar affinity H3 ligand) we decided to test this compound in rats using the SCORE-2000™ assay. We tested ciproxifan maleate at 1 and 3 mg/kg PO in parallel groups of approximately 8-10 rats each. The 1 mg/kg dose administered at CT-5 (mid-sleep phase in the nocturnal rat) exhibited moderate wake-promoting effect that was not further improved by increasing the dose to 3 mg/kg. In addition, ciproxifan was only marginally effective in improving wake consolidation (wake bout lengths), and were starkly inferior to established compounds like caffeine and modafinil (Figure 15).

Taken together, we are not presently bullish about H3 as a wake-promoting therapeutic target. In order for the target to be viable, H3 antagonists will need to demonstrate potent wake-promoting efficacy, which includes increases in wake time and wake consolidation. In their favor, however, we found that H3 antagonists did not cause motor hyperactivity or rebound hypersomnolence. But lack of dose proportionality, poor efficacy, and heterogeneity of the H3 receptor itself presents significant challenges for drug development in this area.

Selective Adenosine A1 antagonists. During the initial AFOSR-PRET Center activity in 1995-2000, clinical activities at the University of Pennsylvania and Harvard University components of the Center assessed the effects of caffeine on neurobehavioral performance and interaction with prior sleep. In the 2000-2005 activity period, the Center's preclinical research revisited adenosine as a target, with focused emphasis on drug action at the adenosine A1 receptor. Caffeine's efficacy as a stimulant derives from activity at four pharmacological targets. It is an antagonist at adenosine A1, adenosine A2, inhibits phosphodiesterase activity, and facilitates calcium mobilization via the intracellular ryanadine receptor. Caffeine's xanthine structure facilitates permeability across cell membranes, allowing for both extracellular and intracellular receptor activity. Paradoxically, however, caffeine has very poor activity at all four targets, with only 40-60 μM affinities. Thus, caffeine's efficacy may rely on the combined effect across all of these targets, or possibly synergistic interaction between two or more of these targets. The published sleep literature has argued that caffeine's wakefulness-promoting activity is most likely mediated primarily by the adenosine A1 receptor. A corollary hypothesis, then would be that sleep homeostasis is physiologically controlled through the A1 receptor. If true, then selective A1 antagonists should be exceptional wake-promoting compounds. Unfortunately, conventional selective A1 antagonists with nanamolar affinity, such as DPCPX (cyclopental substitution on the 8-position of caffeine), have poor brain penetration. Hypnion therefore searched for novel sources of molecules, identifying two different chemical series of non-xanthine A1 and combination A1/A2 antagonists. One of these series was of particular interest as the molecules reportedly have no interaction with ryanadine and phosphodiesterase. Hypnion tested over a dozen compounds with physiologically relevant affinities to A1 using the SCORE-2000™ system. Across these compounds, one chemical series exhibited poor oral bioavailability; however if administered via intraperitoneal injection in rats, showed wake promoting effects that were comparable to, but not superior to, modafinil. Of particular note was our finding that compounds without activity at ryanadine and phosphodiesterase also lacked the prototypical motor side effects (hyperactivity and jitters) characteristic of caffeine. This was an unexpected finding, but was consistent for all A1 and A1/A2 selective compounds without exception. The findings suggest that motor-related adverse events are not "simply" mediated by striatal A1 and A2 receptors, as has been the conventional view. In a second series of adenosine antagonist compounds good oral bioavailablity was observed, with potent wake-promoting effects, no motor effects, and no rebound hypersomnolence when administered to rats at CT-5. For example, doses of 45 mg/kg of HY7050 produced effects comparable to 300 mg/kg modafinil (Figure 16). Diuresis and proconvulsant studies revealed no more potential for these side effects that roughly equipotent doses of caffeine. Together, these findings

seemed promising, and were consistent with the notion that the adenosine receptor could be targeted to selectively promote wakefulness. However, to our surprise, A1 antagonist efficacy decreased dramatically when administered to sleep deprived animals, and disproportionately more so than other wake-promoting targets. The loss of efficacy in the face of sleep deprivation was not viewed as consistent with an ideal medication for sleepiness associated with sustained operations. From a biological perspective, these findings are also not consistent with the hypothesis that A1 mediates physiological sleepiness, an important basic science discovery that will be discussed further, below.

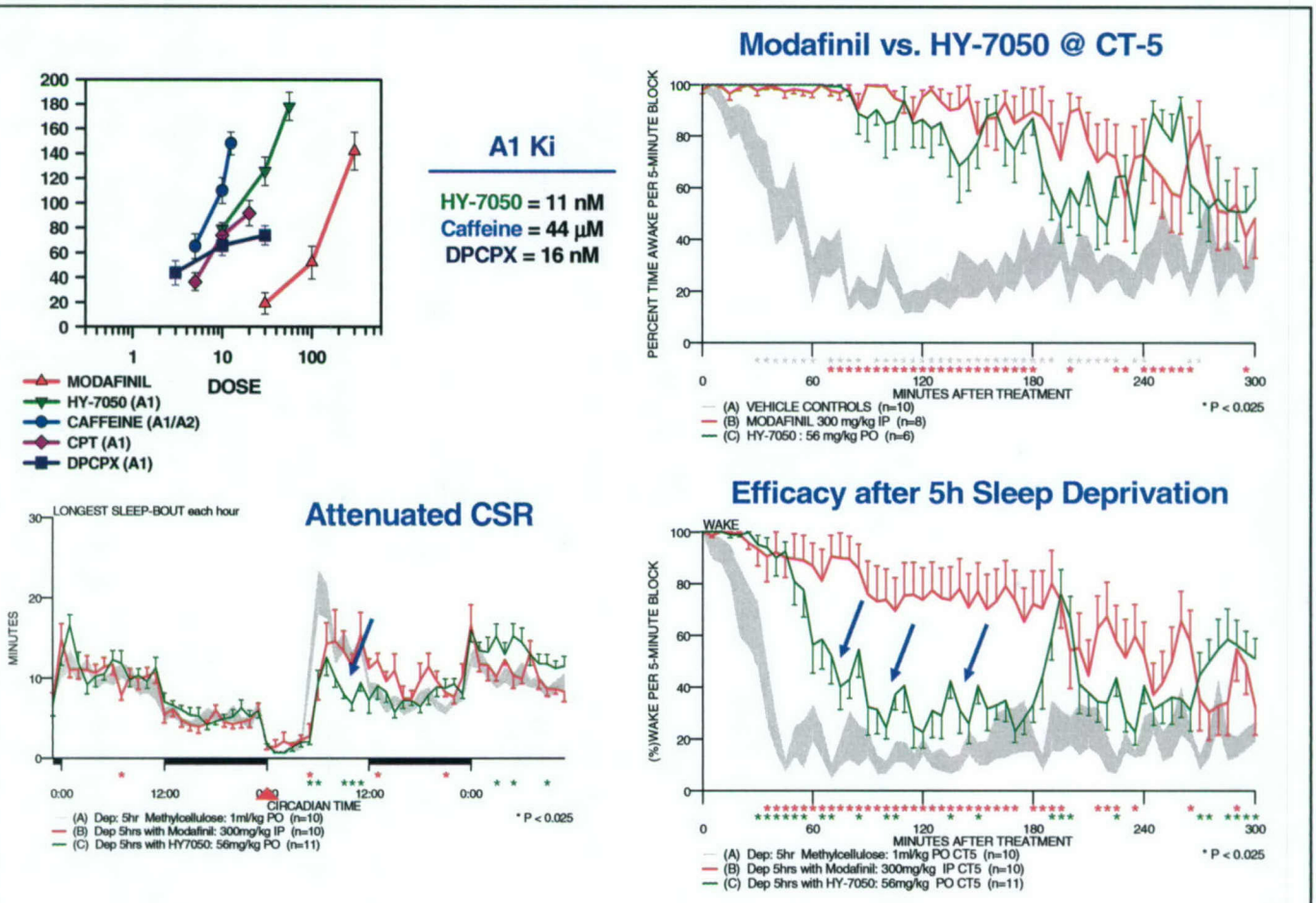

Figure 16. HY-7050, the best in a series of non-xanthine A1 antagonists showed a dramatic loss of efficacy after a moderate duration (5 hours) of sleep deprivation. This finding is not consistent with the notion that the A1 receptor mediates homeostatic sleep drive. CT-5 pharmacodynamic equipotent doses of modafinil (300 mg/kg and HY7050 (56mg/kg; N≥8 per group). HY7050 P<0.0001.

<u>Using sleep deprivation to differentiate wakefulness-promoting compounds</u>. In both night-operations, and in persons subjected to sustained operations, sleep deprivation produces decrements in cognitive throughput and psychomotor vigilance that undermine human performance. Although specific stimulant compounds are sometimes approved for military operations, the nature of stimulant interaction with prior

sleep history is not well established. It is common knowledge that wake-promoting compounds become less effective with increased sleep loss. Indeed, all known sleep and wake compound interact with pre-existing sleep debt. Understanding whether certain classes of wake-promoting agents are more effective in the face of sleep deprivation than others is vital if one is to fully exploit a compounds strengths and understand efficacy in the context of side effects and safety. Such concepts are particularly important to the preclinical identification and differentiation of wakefulness-promoting novel clinical entities. Hypnion developed a standardized preclinical compound differentiation assay system combining conventional SCORE-2000™ efficacy assessments with and without sleep deprivation. The methodology involves two steps. First the dose response curve for a candidate wake-promoting compound administered at CT-5 in laboratory rats is established. For an array of compounds within a chemical scaffold series, or for multiple compounds across different scaffolds, doses of compounds are identified that produce equal net amounts of cumulated wakefulness. For example, at CT-5, 12mg/kg of caffeine, 1 mg/kg of methamphetamine or d-amphetamine, 5mg/kg of methylphenidate, and 300 mg/kg of modafinil all produce the same net amount of accumulated wakefulness (approximately 80-85 minutes net increase adjusted for baseline). Second, the animals are subjected to 5 hours of sustained wakefulness using the automated sleep deprivation apparatus. The sleep deprivation terminates at CT-5 and then the animals are treated with doses of compounds previously determined to be equipotent at CT-5 under non-sleep deprived conditions. Sleep deprivation dramatically differentiates compound efficacy in the face of sleepiness induced by acute sleep deprivation.

Interestingly, we discovered that every adenosine receptor-dependent wake-promoting compound (caffeine, CPT, DPCPX, and over a dozen xanthine and non-xanthine Hypnion A1 antagonist NCEs) lost most of their wake-promoting efficacy in sleep deprived animals. This effect was observed even when the duration of continuous waking was shortened from 5 h to 3 h duration, and applied to selective A1 antagonists (e.g., DPCPX), non-xanthine A1 and mixed A1/A2 antagonists, and xanthaine A1 antagonists. In contrast, the compounds most effective in promoting wakefulness in sleep deprived animals were uniformly of the dopamine transporter inhibition class, and the mixed dopamine and norepinephrine reuptake blockers (DNRIs). We tested one of the better known DNRIs, bupropion, in the sleep deprivation model and contrasted its efficacy to modafinil at doses equipotent under non-sleep deprived conditions. Although high doses of modafinil did very well at promoting wake after sleep deprivation (exceeding the efficacy of caffeine and methylphenidate), bupropion appears to be to be superior to modafinil in this respect. Another impressive feature of bupropion was the compound's lack of rebound hypersomnolence at any time following treatment- even after sleep deprivation. Indeed, the usual compensatory sleep manifestation after sleep deprivation would have been predicted to appear as excessive sleepiness sometime during the 30 hours after sleep deprivation terminated and drug was administered (e.g., at CT-5). However, this was not the case. Taken together, these findings support the notion that mixed noradrenergic and dopamine transport inhibition may be more beneficial in promoting wakefulness than previously realized. Figures 17 and 18 display bupropion data illustrating these points.

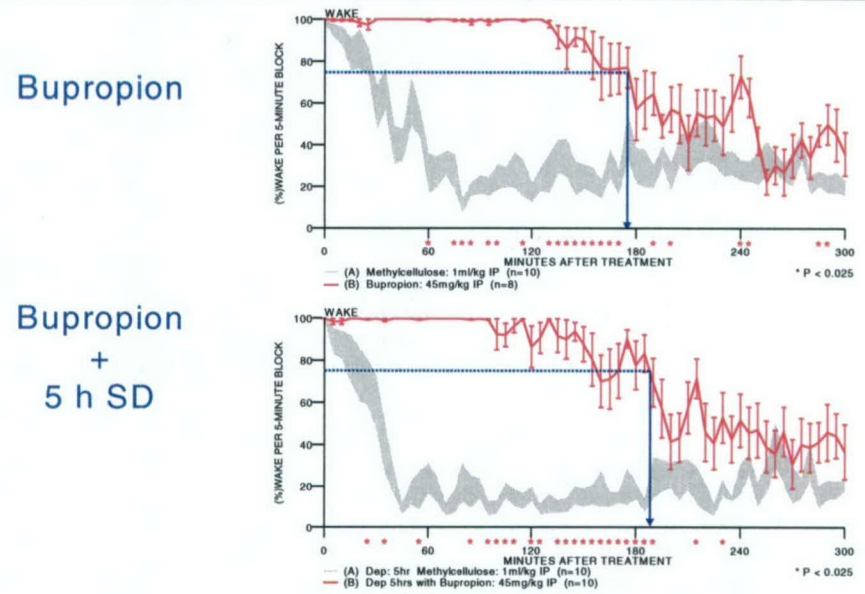

Figure 17. Comparison of bupropion (45 mg/kg IP; N=10 per group) wake promoting efficacy at CT-5 under sleep satiated (upper) and sleep deprived (lower) conditions. Sleep deprivation was imposed for 5 hours from CT-0 to CT-5. The pharmacodynamic AUC of bupropion was ot attenuated by sleep deprivation. In addition, the duration of time that wakefulness was maintained at a level at ot greater than 75% of maximal (e.g., a level exceeding the usual active phase circadian maximum) is illustrated for comparison.

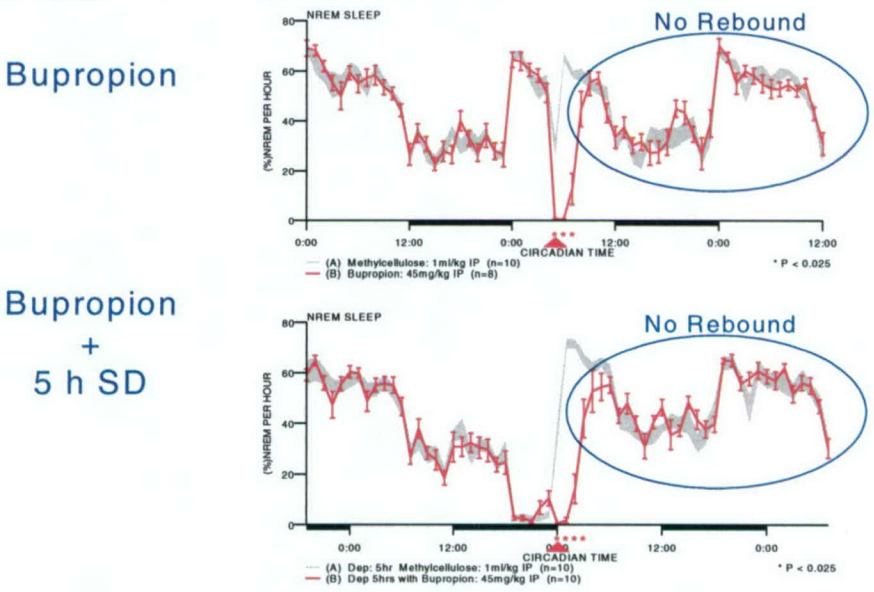

Figure 18. Following the initial 4-hour post-treatment wake-promoting effect, NREM sleep levels returned to vehicle control levels (shaded) in the no sleep deprivation group (upper) and in the 5-hour sleep deprivation group (lower). Note that there was no rebound hypersomnolence from drug-induced wakefulness and, more importantly, from the combined wakefulness due to sleep deprivation and stimulant action.

Stimulant interaction studies. As noted above, there are multiple central pharmacological targets that can engage cortical and behavioral wakefulness. In the context of the Opponent Process Model, we hypothesized that the application of pharmacological agents targeted to increase SCN-dependent alerting together with the application of pharmacological agents that attenuate homeostatic sleep drive could produce more effective wake promotion with fewer side effects than any single approach. Our approach to this hypothesis was to treat laboratory rats with combinations of compounds with known waking effects, or with compounds hypothesized to have mechanistic rational for synergistic interaction (e.g., using a MAO-B inhibitor in combination with a weak dopamine transport inhibitor like modafinil). The nature of these studies required considerable work and resources, as the wake promoting properties in combination with vehicle had to be separately characterized to all for adequate treatment controls. Initially we studies modafinil in combination with adenosine antagonists (caffeine, DPCPX, HY7048) , SSRI antidepressants (fluoxetine, paroxetine), DNRI compounds (bupropion), and the irreversible MAO-B inhibitor selegline using a screening approach. The dose of modafinil (30mg/kg) used was suprathreshold to facilitate detection of synergism. We also tested a range of dses of d-amphetamine in combination with caffeine. Finally we tested comninations of the prototypical dopamine transporter inhibitor GBR12909 with the noradrenergic reuptake blocker nisoxetine, with caffeine, with the selective A1 antagonist DPCPX and with the SSRI paroxetine. A summary of the principal conclusions of these experiments is provided in the Table, above. Most of the combination treatments produced additive wake-promoting effects based on pharmacodynamic AUC. Slightly super-additive wake promoting effects were observed for modafinil + caffeine combinations and modafinil + paroxetine combinations. Interestingly. D-amphetamine + caffeine combinations were consistently sub-additive, producing less net wakefulness than the sum of the individual drug effects. Of the many drug interaction experiments that were performed, only one combination produced synergistic interaction based on pharmacodynamic AUC—GBR12920 + paroxetine. These results for summarized in Table 8.

Table 8. Wake-promoting effects of different drug combinations.

Modafinil 30 + Bupropion 10 IP	additive
Modafinil 30 + Caffeine 3, 5 IP	weak synergy
Modafinil 30 + DPCPX 3 IP	additive
Modafinil 30 + HY7048 30 IP	additive
Modafinil 30 + Fluoxetine 5 IP	additive
Modafinil 30 + Paroxetine 1	weak synergy
Modafinil 30 + Selegline 0.25	additive
d-amphetamine 0.5, 1.5 + Caffeine 5, 10 IP	sub-additive
GBR12909 10 + Nisoxetine 2 IP	additive
GBR12909 2.5, 5, 10 + Caffeine 5,10 IP	additive
GBR12909 5 + DPCPX 3 IP	additive
GBR12909 2.5, 10 + paroxetine 2.5, 5 IP	synergistic *

Doses (mg/kg) were administered in all combinations.

Figure 19 reveals that the dopamine transport inhibitor GBR12909 administered together with the SSRI paroxetine produced impressive levels of wakefulness that were spontaneously sustained for upwards of 4 hours (which is extraordinary in a polyphasic sleep species like the rat). Isobolographic analysis revealed the greatest synergism from GBR 10omg/kg + paroxetine 5 mg/kg. We do not yet have a neurobiological hypothesis to explain this synergism. One possibility is that a particular combination of strong SSRI and relatively weak norepinephrine uptake inhibition associated with paroxetine in combination with the dopamine and norepinephrine transport inhibition properties of GBR12909 create an optimized dopamine and noradrenergic transmission ratio to engage waking and forebrain attention mechanisms. However, there are alternative explanations that will require further evaluation. In the present studies we have applied clinical definitions of efficacy, which are based on net improvement in the amount of wakefulness over time— what we refer to as the pharmacodynamic wake AUC. It is plausible, however, that the combination of compounds interact to slow the relative rates of metabolism and/or excretion of one or both, thereby increasing the terminal half life of the treatment independent of efficacy. Because the individual component compounds each increase wakefulness to 100% time per hour, the combination of effects can not be quantitatively gauged on an intensity scale. Thus, once an animal is awake 100% time, alternative methods are needed to evaluate the efficacy action spectrum. In future studies, we plan to evaluate combination drug effects in sleep deprived animals using the SCORE-2000™ automated sleep deprivation technology. Using this approach, increasing amounts of sleep deprivation can be applied to better assay for the intensity of wake-promoting effect. This approach may also provide better insight into the suitability of combination therapeutic countermeasures for sleepiness due to sustained operations.

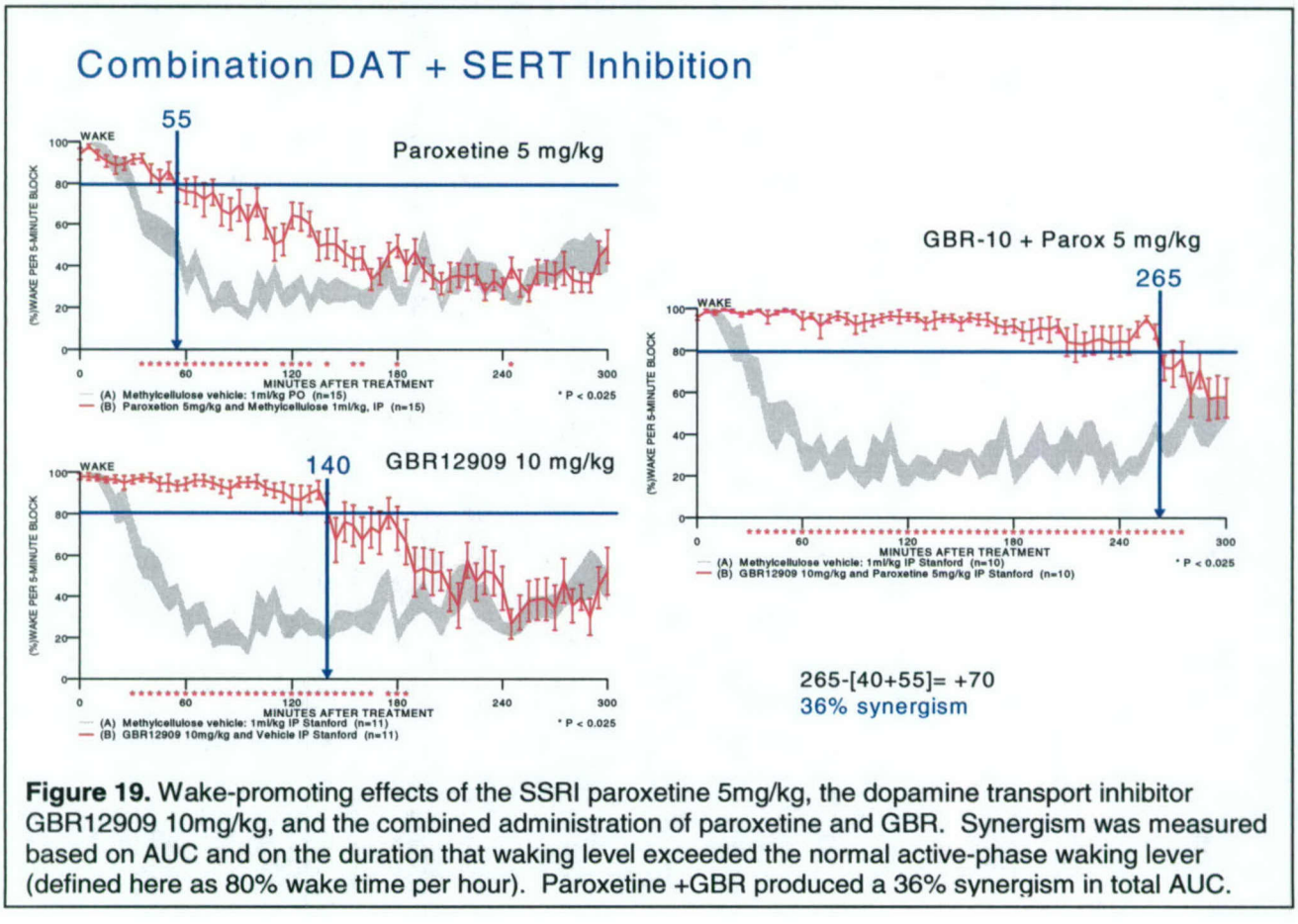

Figure 19. Wake-promoting effects of the SSRI paroxetine 5mg/kg, the dopamine transport inhibitor GBR12909 10mg/kg, and the combined administration of paroxetine and GBR. Synergism was measured based on AUC and on the duration that waking level exceeded the normal active-phase waking lever (defined here as 80% wake time per hour). Paroxetine +GBR produced a 36% synergism in total AUC.

5. PERSONNEL SUPPORTED/AND OR ASSOCIATED WITH THE PRET CENTER RESEARCH EFFORT

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Julia Cunningham	Behavioral Monitor
Rachel Dailey	Behavioral Monitor
Megan Daney	Behavioral Monitor
Kimberly Dasch	Behavioral Monitor
Deana Davis	Behavioral Monitor
Rachel Dlugash	Behavioral Monitor
Jeffrey Eisenstein	Behavioral Monitor
Rebecca Elwork	Behavioral Monitor
Sophia Feller	Behavioral Monitor
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Pooja Lakshmin	Behavioral Monitor
Chau Wing Lam	Behavioral Monitor
Hillary Lazarus	Behavioral Monitor
Jason Lee	Behavioral Monitor
Paul Lewis	Behavioral Monitor
Alice Lin	Behavioral Monitor
Ryan Macht	Behavioral Monitor
Danielle Mangino	Behavioral Monitor
Polina Mamontov	Behavioral Monitor
Brian Matthews	Behavioral Monitor
Alexander McCauly	Behavioral Monitor
Carrie McCloskey	Behavioral Monitor
Robert McNeary	Behavioral Monitor
Jessica Mills	Behavioral Monitor
Joyce Minakami	Behavioral Monitor
Mark Mitchell	Behavioral Monitor
Eleanor Monett	Behavioral Monitor
Harry Moroz	Behavioral Monitor
Jessica Morris	Behavioral Monitor
Jennifer Nguyen	Behavioral Monitor
Ngoc Nguyen	Behavioral Monitor
Bradley Olson	Behavioral Monitor
Yaniz Padilla	Behavioral Monitor
Gina Paek	Behavioral Monitor
Corinna Panlilio	Behavioral Monitor
Bertrand Parcells	Behavioral Monitor
Ami Patel	Behavioral Monitor
Anita Patel	Behavioral Monitor
Langston Payne	Behavioral Monitor
Tejas Patil	Behavioral Monitor
Maggie Phan	Behavioral Monitor
Miriam Pogach	Behavioral Monitor
Mariel Poole	Behavioral Monitor
Alan Powers	Behavioral Monitor
Shawn Puri	Behavioral Monitor
Cristin Rabik	Behavioral Monitor
Shankar Rajeswaran	Behavioral Monitor
Alifiya Rangwala	Behavioral Monitor
Aarif Rassiwalla	Behavioral Monitor
Farid Razavi	Behavioral Monitor
Catriona Revell	Behavioral Monitor

Samuel Rikoon	Behavioral Monitor
Jenna Rimberg	Behavioral Monitor
Elizabeth Rossin	Behavioral Monitor
Luz-Adriana Samper	Behavioral Monitor
Puja Saxena	Behavioral Monitor
Candance Schoengold	Behavioral Monitor
Jeffrey Schoengold	Behavioral Monitor
Maureen Schriver	Behavioral Monitor
Matthew Schwartz	Behavioral Monitor
Robin Seila	Behavioral Monitor
Neha Shah	Behavioral Monitor
Christine Shin	Behavioral Monitor
Rebecca Shore	Behavioral Monitor
Komal Soin	Behavioral Monitor
Jill Starzyk	Behavioral Monitor
Petra Stewart	Behavioral Monitor
Jay Sy	Behavioral Monitor
Sheida Tabaie	Behavioral Monitor
Erin Tompkins	Behavioral Monitor
Priyanka Tulshian	Behavioral Monitor
Harvin Vig	Behavioral Monitor
Michelle Wallenstein	Behavioral Monitor
Elena Weinreb	Behavioral Monitor
Timothy Wilkins	Behavioral Monitor
Kate Winterkorn	Behavioral Monitor
Hye-In Yoon	Behavioral Monitor
Alyssa Zackler	Behavioral Monitor
Shawn Zhou	Behavioral Monitor

Harvard University:

Charles A. Czeisler, Ph.D. M.D.	Professor of Medicine
Scott Grady, M.D.	Clinical Research Fellow
Kenneth P. Wright Jr., Ph.D.	Assistant Professor
Daniel Aeschbach, Ph.D.	Neuroscientist/Assistant Professor of Medicine
Elizabeth Klerman, M.D., Ph.D.	Physician, Assistant Professor in Medicine
Dennis Dean	IS Programmer Analyst Sr.
Kathrine Gurdziel	IS Programmer Analyst
Brandon Lockyer	PSG Technician Sr.
Eymard Riel	PSG Technician
Mary Carol Mazza	Research Assistant
Sara Penchincar	Research Assistant
Gregg Renchkovsky	Research Assistant
Melissa St. Hilaire	Research Assistant
Luana DelVecchio	Executive Administrative Assistant

Stanford University (2000-2002):

Dale M. Edgar, Ph.D.	Associate Professor of Psychiatry & Behavioral Science
Jonathan P. Wisor, Ph.D.	Research Scientist, Stanford University
Emmanuel Mignot, Ph.D.	Professor, Stanford University

Hypnion, Inc. (2000-2005):

Dale M. Edgar, Ph.D.	SVP and Chief Science & Technology Officer
Michael Fitzgerald	VP Finance & Administration
James F. White, Ph.D.	EVP Drug Discovery
Dorothy Griffiths	Executive Administrative Assistant
Dianne Bennett	Administrative Assistant
Dawn Kemp	Administrative Assistant
Wesley F. Seidel	SCORE Projects Manager
Paul Gregory	Manager, Life Sciences Group
Nicholas Guise	Director, Life Sciences
Thomas Kulp, Ph.D.	Head, Biostatistics Group
Lin Lee	Certified SAS Data Analyst
Chaing Hou	Database & SAS Software Engineer
Tom Kirby	Head, Information Technology Group
Rand Wheatland	SCORE-2000 System Programmer
Marc Allen	Programmer Analyst
Christine Lawrence	Programmer
Aaron Wise	IT/IS Engineer and Data Security Officer
Bryan Mills	Head, DBD/DBA Group
Gary DesRoches	Software Engineer
George Kelley	Sr. Software Engineer
Robert Delsignore	Head, Engineering Group
William Morris	Sr. Engineering Technician
Robert Pedone	Sr. Electronics Technician
Patrick Philbin	Head, Engineering Group
Rot Tran	Electronics Technician
Linda Tran	Electronics Technician
Clara Kebabian	Research Data/Materials Coordinator
Daniel Aleksandrowicz	Research Associate
Keith Halley	Research Associate
Hilary Stanley	Research Associate
Jenifer Scafifi	Research Associate
Katherine Green	Research Associate
Christina Maiuri	Supervisor, Research Associates & Technicians
Alex Talarico	Research Technician
Liane Julianello	Research Technician
Barry Dussault	Compliance Officer
Bret Tallent	Manager, ARF Operations
Dawn Hidenfelter	Supervisor, Animal Resources Facility
Eddie Costa	Animal Care Technician
Michael Power	Animal Care Technician

Scientific Consultants to Hypnion, Inc. (2000-2005):

Prof. Dr. Henk Timmerman	Vrije University, Amsterdam
David Leander, Ph.D.	Sr. Research Fellow, Lilly Neuroscience (retired)

6. PUBLICATIONS (2000 - 2005)

6A. 2000-2005 Total N =54 Journal articles, chapters, reviews, dissertations supported in whole or in part by the Center

2000 (n = 2) Journal articles, chapters, reviews, dissertations

Kas, M.J.H., and D.M. Edgar. Photic phase response curve in Octodon degus: assessment as a function of activity phase preference. Am. J. Physiol. 278: R1385-R1389, 2000.

Van Dongen, H.P.A., Brodnyan, C.G., MacAdam, H.L., Dinges, D.F.: Sleep architecture of nighttime and daytime naps during 88 hours of extended wakefulness. Sleep-Wake Research in The Netherlands 11: 48-52, 2000.

2001 (n = 14) Journal articles, chapters, reviews, dissertations

Doran, S.M., Van Dongen, H.P.A., Dinges, D.F.: Sustained attention performance during sleep deprivation: Evidence of state instability. Archives Italiennes de Biologie, 13: 1-15, 2001.

Dinges, D.F.: Stress, fatigue, and behavioral energy. Nutrition Reviews, 59(1): S30-S32, 2001.

Kas, M.J.H., and D.M. Edgar. Scheduled voluntary wheel running activity modulates free-running circadian body temperature rhythms in Octodon degus. J. Biol. Rhythms 16: 66-75, 2001.

Meier Ewert, H.K., Ridker, P.M., Rifai, N., Price, N., Dinges, D.F., Mullington, J.M.: Absence of diurnal variation of C-reactive protein. Clinical Chemistry, 47: 426-430, 2001.

Rogers, N.L., Dinges, D.F.: Shiftwork, circadian disruption, and consequences. The Economics of Neuroscience, 3(9): 1-7, 2001.

Rogers, N.L., Szuba, M.P., Staab, J.P., Evans, D.L., Dinges, D.F.: Neuroimmunologic aspects of sleep and sleep loss. Seminars in Clinical Neuropsychiatry, 6(4): 2001.

Rogers, N.L., Szuba, M.P., Staab, J.P., Evans, D.L., Dinges, D.F. Sleep, sleep loss and immune function in humans. Seminars in Clinical Neuropsychiatry, 6(4):295-307, 2001.

Rogers, N.L., Dinges, D.F. Shiftwork, circadian disruption and consequences. The Economics of Neuroscience, 6(7): 58-64, 2001.

Shearer, W.T., Reuben, J.M., Mullington, J.M., Price, N.J., Lee, B., Smith, E.O., Szuba, M.P., Van Dongen, H.P.A., Dinges, D.F.: Soluble tumor necrosis factor-alpha receptor 1 and interleukin-6 plasma levels in humans subjected to the sleep deprivation model of space flight. The Journal of Allergy and Clinical Immunology, 107: 165-170, 2001.

Van Dongen, H.P.A., Dinges, D.F. Sleep deprivation and circadian misalignment: Stressors that are the same for everyone? Annals of the symposium Stressor-Induced Alterations in Sleep, Sao Paulo, Brazil: 27-36, 2001.

Van Dongen, H.P.A., Dinges, D.F. Circadian and homeostatic interactions in waking neurobehavioral functions during partial and total sleep deprivation: Effects of caffeine. In Institute of Medicine, Caffeine for the sustainment of mental task performance. National Academy Press, Washington, D.C., p. 127, 2001.

Van Dongen, H.P.A., Price, N.J., Mullington, J.M., Szuba, M.P., Kapoor, S.C. Dinges, D.F. Caffeine eliminates psychomotor vigilance deficits from sleep inertia. Sleep 24(7): 813-819, 2001.

Van Dongen, H.P.A., Price, N.J., Mullington, J.M., Szuba, M.P., Kapoor, S.C., Dinges, D.F.: Caffeine eliminates psychomotor vigilance deficits from sleep inertia. Sleep 24 (7):813-819, 2001.

Wisor, J..P., S. Nishino, I. Sora, G.H. Uhl, E. Mignot, and D.M. Edgar. Dopaminergic role in stimulant-induced wakefulness. J. Neuroscience, 21(5):1787-1784, 2001.

2002 (n = 6) Journal articles, chapters, reviews, dissertations

Dinges, D.F.: Neurobehavioral characteristics of sleepiness and fatigue. Clinical Psychiatry News (S): 5-8, 2002.

Kloss, J.D., Szuba, M.P., Dinges, D.F.: Sleep Loss and Sleepiness: Physiological and Neurobehavioral Effects. (Chapter 130) in Davis, K.L., Charney, D., Coyle, J.T., Nemeroff (Eds.) in Neuropsychopharmacology: The Fifth Generation of Progress, Lippincott Williams & Wilkins, Philadelphia, pp.1895-1907, 2002.

Neri, D.F., Oyung, R.L., Colletti, L.M., Mallis, M.M., Tam, P.Y., Dinges, D.F.: Controlled breaks as a fatigue countermeasure on the flight deck. Aviation Space & Environmental Medicine 73 (7):654-664, 2002.

Rogers, N. L., Dinges, D. F. Shiftwork, circadian disruption and consequences. Primary Psychiatry 9(8):50-56, 2002.

Wisor, J.P., B.F. O'Hara, A. Terao, C.P. Selby, T.S. Kilduff, A. Sancar, D.M. Edgar and P. Franken. A role for cryptochromes in sleep regulation. BMC Neurosci. 20;3(1):20.

Epub 2002.

Wisor, J.P., T.M. Delorey, G.E. Homanics and D.M. Edgar. Sleep states and sleep electroencephalographic spectral power in mice lacking the B3 subunit of the GABAA receptor. Brain Research, 955(1-2):221-228, 2002.

2003 (n = 11) Journal articles, chapters, reviews, dissertations

Dinges D.F., Weaver T.E. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. Sleep Med. 4(5):393-402, 2003.

Mullington, J.M., Chan, J.L., Van Dongen, H.P.A., Szuba, M.P., Samaras, J., Price, N.J., Meier-Ewert, H.K., Dinges, D. F., Mantzoros, C.S. Sleep loss reduces diurnal rhythm amplitude of leptin in healthy men. Journal of Neuroendocrinology 15(9): 851-854, 2003.

Rogers, N. L., Kennaway, D. J, Dawson, D. Neurobehavioural performance effects of daytime melatonin and temazepam administration. Journal of Sleep Research 12(3):1-6, 2003.

Rogers, N.L., Dorrian, J., Dinges, D.F.: Sleep, waking and neurobehavioural performance. Frontiers in Bioscience 8:1056-1067, 2003.

Van Dongen, H.P.A., Maislin, G., Mullington, J.M., Dinges, D. F. Rapid publication: The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26: 117-126, 2003.

Van Dongen, H.P.A., Rogers, N.L., Dinges, D.F. Understanding sleep debt: Theoretical and empirical issues. Sleep and Biological Rhythms 1: 5-13, 2003.

Van Dongen, H.P.A., Dinges, D.F. Investigating the interaction between the homeostatic and circadian processes of sleep-wake regulation for the prediction of waking neurobehavioral performance. Journal of Sleep Research; 12 (3): 181-187, 2003.

Van Dongen, H.P.A., Maislin, G., Mullington, J.M., Dinges, D. F. Rapid publication: The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep, 26: 117-126, 2003.

Van Dongen, H.P.A., Maislin, G., Mullington, J.M., Dinges, D.F.: The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26 (2):117-126, 2003.

Van Dongen, H.P.A., Rogers, N.L., Dinges, D.F.: Sleep debt: Theoretical and empirical issues. Sleep and Biological Rhythms 1:5-13, 2003.

Wisor, J.P., S.W. Wurts, F.S. Hall, K.P. Lesch, D.L. Murphy, G.R. Uhl, and D.M. Edgar. Altered rapid eye movement (REM) sleep timing and REM-related EEG spectra in serotonin transporter knockout mice. Neuroreport 14(2): 1-6, 2003.

2004 (n = 6) Journal articles, chapters, reviews, dissertations

Ballas, C., Evans, D.L., Dinges, D.F.: Amphetamine, Methylphenidate and Modafinil. In: Schatzberg, A.F. and Nemeroff, C.B. (Eds.) Textbook of Psychopharmacology (3rd edition), American Psychiatric Publishing, Washington, DC, pp. 671-684, 2004.

Dinges, D.F. Critical research issues in development of biomathematical models of fatigue and performance. Aviation, Space & Environmental Medicine 75 (3):A181-A191, 2004.

Dinges, D.F.: Critical research issues in development of biomathematical models of fatigue and performance. Aviation, Space and Environmental Medicine 75 (3):A181-A191, 2004.

Meier-Ewert, H., Ridker, P.M., Rifai, N., Regan, M.M.., Price, N., Dinges, D.F., Mullington, J.M.: Effects of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. Journal of the American College of Cardiology 43:678-683, 2004.

Van Dongen, H.P.A. Comparison of mathematical model predictions to experimental data of fatigue and performance. Aviation, Space, & Environmental Medicine, 75 (3, Suppl.): A15-36, 2004.

Van Dongen, H.P.A., Olofsen, E., Dinges, D.F., Maislin, G.: Mixed-model regression analysis and dealing with interindividual differences. In: Johnson, M.L., Brand, L. (Eds.) Numerical computer methods, part E. Methods in Enzymology 384, Academic Press, Amsterdam, 10:139-171, 2004.

2005 (n = 14) Journal articles, chapters, reviews, dissertations (in press & submitted)

Durmer, J.S. and Dinges, D.F.: Neurocognitive consequences of sleep deprivation. Seminars in Neurology, 25(1):117-129, 2005.

Dorrian, J., Rogers, N.L., Dinges, D.F.: Psychomotor vigilance performance: A neurocognitive assay sensitive to sleep loss. In: Kushida, C. (Ed.), Sleep Deprivation: Clinical Issues, Pharmacology and Sleep Loss Effects. Marcel Dekker, Inc., New York, NY, pp. 39-70, 2005.

Rogers, N. L., Kloss, J. D. Medical conditions and diseases. In: Kushida, C. (Ed.) Sleep Deprivation, Marcel Dekker, NY, pp. 81-119, 2005.

Van Dongen, H.P.A., Dinges, D.F.: Sleep, circadian rhythms, and psychomotor vigilance performance. Journal for Clinics in Sports Medicine 24:237-249, 2005

Rogers, N.L., Dinges, D.F.: Caffeine: Implications for alertness in athletes. Journal for Clinics in Sports Medicine 24:1-13, 2005.

Czeisler, C.A., Walsh, J.K., Roth, T., Hughes, R.J., Wright, K.P., Kingsbury, L., Arora, S., Schwartz, J.R.L., Niebler, G., Dinges, D.F.: Modafinil for excessive sleepiness associated with shift work sleep disorder. New England Journal of Medicine, 353:476-486, 2005.

Drummond, S.P.A., Bischoff-Grethe, A., Dinges, D.F., Ayalon, L., Mednick, S.C., Meloy, M.J.: The neural basis of the psychomotor vigilance task. Sleep 28(9):1059-1068, 2005.

Bonnet, MH, Balkin, TJ, Dinges, DF, Roehrs, T, Rogers, NL, Wesensten, NJ: The use of stimulants to modify performance during sleep loss: A review by the Sleep Deprivation and Stimulant Task Force of the American Academy of Sleep Medicine. Sleep, 28(9):1163-1187, 2005.

Klerman EB, Dijk D-J. Inter-individual variation in sleep duration and its association with sleep debt in young adults. Sleep. 28(10):1253-1259, 2005.

Dinges, D.F. Can habitual sleep duration harbor sleep debt? Sleep 28(10):1208-1209, 2005.

Avinash, D, CP Crudele, DD Amin, BM Robinson, DF Dinges, HPA Van Dongen. Parameter estimation for a biomathematical model of psychomotor vigilance performance under laboratory conditions of chronic sleep restriction. Sleep-Wake Research in The Netherlands, in press.

Dinges, D.F., Rogers, N.L. The Future of Human Intelligence: Enhancing Cognitive Capability in a 24/7 World, Proceedings of the 3rd International Spearman Seminar Extending Intelligence: Enhancement and New Constructs, in press.

Indic P, Forger DB, St. Hilaire MA, Dean DA II, Brown EN, Kronauer RE, Klerman EB, Jewett ME. Comparison of amplitude recovery dynamics of two limit cycle oscillator models of the human circadian pacemaker. Chronobiology International, in press.

Van Dongen, HPA, JA Caldwell, JL Caldwell. Investigating systematic individual differences in sleep-deprived performance on a high-fidelity flight simulator. Behavior Research Methods, in press.

6B. 2000-2005 Total N = 52 Abstracts supported in whole or in part by the Center

2000 (n = 1) Abstracts

Van Dongen, H.P., Doran, S.M., MacAdam, H.L., Szuba, M.P., Dinges, D.F.: Sleep Inertia: Effects of homeostatic drive, circadian rhythm, and caffeine. Journal of Sleep Research 9 (Suppl. 1): 197, 2000.

2001 (n = 18) Abstracts

Atzram, M., Chow, C., Price, N.J.., Rogers, N.L., Van Dongen, H., Dinges, D.F.: Can sleep attacks occur without feeling sleepy? Sleep, 24S: A428, 2001.

Dinges, D.F., Maislin, G., Van Dongen, H.: Chronic sleep restriction: relation of sleep structure to daytime sleepiness and performance. Sleep, 24S: A28, 2001.

Gooneratne, N.S., Weaver, T.E., Maislin, G., Pack, F., Arner, H., Dinges, D.F., Pack, A.I.: A comparison of the Epworth Sleepiness Scale and the Functional Outcomes of Sleepiness Questionnaire in the assessment of excessive daytime sleepiness in the elderly. Sleep, 24S: A233, 2001.

Hughes, R.J., Van Dongen, H., Dinges, D.F., Rogers, N., Wright Jr., K.P., Edgar, D.F., Czeisler, C.A.: Modafinil improves alertness and performance during simulated night work. Sleep, 24S: A200, 2001.

Maislin, G., Pack, A., Samuel, S., Dinges, D.F.: Objectively measured sleep behaviors and vigilance in community residing elderly with and without complaints of daytime sleepiness. Sleep, 24S: A224, 2001.

Maislin, G., Rogers, N.L., Price, N.J., Mullington, J.M., Szuba, M.P., Van Dongen, H.P., Dinges, D.F.: Response surface modeling of the effects of chronic sleep restriction with and without diurnal naps. Sleep 24S: A242, 2001.

Mallis, M.M., Neri, D.F., Oyung, R., Colletti, L., Nguyen, T., Dinges, D.F.: Factors associated with behavioral alertness in pilots flying simulated night flights. Sleep 24S: A123, 2001.

McConnell, K.J., Maislin, G., Rogers, N.L., Price, N.J., Mullington, J.M., Szuba, M.P., Brodnyan, C.G., Cerceo, L., Van Dongen, H., Dinges, D.F.: Sleep efficiency during chronic nocturnal sleep restriction with and without diurnal naps. Sleep 24S: A431, 2001.

Orthmann, J.L., Rogers, N.L., Price N.J., Mullington, J.M., Szuba, M.P., Van Dongen, H., Dinges, D.F.: Changes in plasma growth hormone levels following chronic sleep restriction. Sleep 24S: A248, 2001.

Pack, A.I., Maislin, G., Staley, B., George, C., Pack, F.M., Dinges, D.F.: Factors associated with daytime sleepiness and performance in a sample of commercial drivers. Sleep 24S: A427, 2001.

Pack, A.I., Maislin, G., Staley, B., Pack, F.M., Dinges, D.F.: Sleep duration at home in a sample of commercial drivers. Sleep 24S: A247, 2001.

Price, N.J., Rogers, N.L., Szuba, M.P., Van Dongen, H., Dinges, D.F.: Recovery from sleep deprivation: effects of sleep duration and number of nights. Sleep 24S: A30, 2001.

Rapaport, B.S., Powell, J.W., Dinges, D.F., Van Dongen, H.: Digit-symbol substitution task: learning and sleep. Sleep 24S: A240, 2001.

Rogers, N.L., Price N.J., Szuba, M.P., Van Dongen, H.P, Dinges, D.F.: Effect of sustained caffeine of core body temperature during a 88 hours of sustained wakefulness. Sleep 24S: A172, 2001.

Shah, A.D., Van Dongen, J., Maislin, G., Brodnyan, C.G., Dinges, D.F.: Dynamics of slow-wave activity during chronically restricted sleep. Sleep 24S: A247, 2001.

Van Dongen, H., Maislin, G., Dinges, D.F.: Statistical Modeling of the waking neurobehavioral response to chronic partial sleep deprivation. Sleep 24S: A245, 2001.

Van Dongen, H., Maislin, G., Hachadoorian, B., Dinges, D.F.: A statistical model of cumulative sleep debt in chronic sleep restriction. Sleep 24S: A28, 2001.

Dean II DA, Jewett ME. Circadian Performance Simulation Software (CPSS) provides a tool for validation of circadian and neurobehavioral mathematical models. Sleep, A103, 2001.

2002 (n = 7) Abstracts

Cajochen C., Wyatt J.K., Czeisler C.A., Dijk D.-J. Separation of circadian and sleep and wake duration-dependent modulation of EEG activation during wakefulness. Neuroscience 114:1047, 2002.

Dean II, DA , Jewett, ME. Effects of light pulse duration and intensity in model simulations of human phase response curves. Association of Professional Sleep Societies, A427, 2002.

Dorrian J., Rogers N.L., Ryan C., Dinges C.M., Szuba M.P., Dinges D.F. Comparing the effects of total sleep deprivation and chronically restricted diurnal sleep on prefrontal neuropsychological functioning. Sleep, 25 (Suppl.):A444-A445, 2002.

Gray AR, Dean, DA, Horowitz TS, Barger LK, Jewett ME. With limited input data, Kronauer's light model makes accurate circadian phase predictions on average, but

makes large errors in some individual predictions. Sleep 25: A422, 2002.

May, C, Dean II, DA, Jewett, ME, A new mathematical definition of CBT_{min} improves model predictions of the effect of light on the circadian pacemaker in amplitude suppression protocols. Society for Research on Biological Rhythms, 133, 2002.

Price, N.J., Rogers, N.L., Fox, C.G., Szuba, M.P., Van Dongen, H.P. Dinges, D.F. Sleep physiology following 88h total sleep deprivation: Effects of recovery sleep duration. Sleep 5(Suppl. 1): A92-A93, 2002.

Van Dongen, H.P.A. Dinges, D.F. Chronic partial sleep deprivation data point to a novel process regulating waking behavioural alertness. Journal of Sleep Research 11(Suppl. 1): 232, 2002.

2003 (n = 7) Abstracts

Crabbe, J. B., Rogers, N. L., Szuba, M. P., Dinges, D. F. Modafinil does not affect heart rate or heart rate variabilityfrom 0800-1200 hours during 88 hours of simulated sustained operations Sleep 26(Suppl.): A173-A174, 2003.

Dorrian, J., Rogers, N. L., Ryan, C., Dinges, C. M., Szuba, M. P., Jones, C. J., Dinges, D. F. Total sleep deprivation and chronic diurnal sleep restriction similarly affect an index of prefrontal function, Internal Medicine Journal, 2003.

Maislin, G., Van Dongen, H. P. A., Rogers, N.L., Dinges, D.F. Statistical modeling of responses over time in sleep restriction protocols. Sleep 26(Suppl.): A442-A443, 2003.

O'Meara, K. O., Rogers, N. L., Dorrian, J., Szuba, M. P., Dinges, D. F. Effects of modafinil on symptom reports during 88 hours of simulated sustained operations. Sleep 26(Suppl.): A181, 2003.

Rider, R. L., G. Maislin, Fox, C. G., N. Rogers, D.F. Dinges Assessment of the effects of modafinil on sleep during 88 hours of sustained operations, Sleep 26(Suppl.): A191, 2003.

Rogers, N. L., Maislin, G., Van Dongen, H. P. A., Dinges, D. F. Neurobehavioural and physiological outcomes from modafinil during severe sleep loss, Internal Medicine Journal, 2003.

Rogers, N.L., Van Dongen, H.P.A., Powell, IV, J.W., Carlin, M.M., Szuba, M.P., Maislin, G. and Dinges, D.F. Neurobehavioural functioning during 88 hours of sustained operations: Naps and modafinil as countermeasures, Sleep 26(Suppl.): A178, 2003.

2004 (n = 13) Abstracts

Baffy, N.J., Rogers, N.L., Van Dongen, H., Dinges, D.F.: Age effects on neurobehavioral speed before and after sleep deprivation in healthy adults. Sleep 27 (Abstract supplement): A155, 2004.

D. A. Dean II, M. C. Mazza, J.K. Wyatt, C.A. Czeisler, E. B. Klerman· Circadian and Homeostatic Components of Mathematical Models of Neurobehavioral Performance for the Effects of Low Dose Caffeine During a 42-Hour Forced Desynchrony Protocol. Sleep 2004

Dorrian, J., Rogers, N. L., Ryan, C., Dinges, C. M., Szuba, M. P., Jones, C. J., Dinges, D. F. Total sleep deprivation and chronic diurnal sleep restriction similarly affect an index of prefrontal function. Internal Medicine Journal 34: A19, 2004.

Maislin, G., Rogers, N.L., Gooneratne, N., Pack, A.I., Dinges, D.F.: A convergence algorithm for objective determination of dim light Melatonin onset (DLMO). Sleep 27 (Abstract supplement): A73, 2004.

Niyogi, S., Maislin, G., Ballas, C., Rogers, N., Van Dongen, H.P., Dinges, D.F.: Effects of a daily dose of Modafinil during sustained operations. Aviation, Space, and Environmental Medicine 75(4): B10, 2004.

Niyogi, S., Rogers, N.L., Dinges, D.F.: Effect of extended wakefulness and recovery sleep on thyroid axis activity. Sleep 27 (Abstract supplement): A151, 2004.

O'Connor, R.M., Rogers, N.L, Van Dongen, H., Dinges, D.F.: Dose response effects of short duration naps during extended wakefulness. Sleep 27 (Abstract supplement): A155, 2004.

O'Connor, R.M., Van Dongen, H.P., Rogers, N.L., Price, N., Szuba, M., and Dinges, D.F.: Comparison of the separate and combined effects of caffeine and prophylactic naps during sustained operations. Aviation, Space, and Environmental Medicine 75(4): B11, 2004.

Price, N.J., Rogers,, N.L., Fox, C.G., Dinges, D.F.: Correlations between sleep physiology and neurobehavioral performance following recovery from 88h total sleep deprivation. Sleep 27 (Abstract supplement): A152, 2004.

Rogers NL, Maislin G, Van Dongen HPA, Dinges DF. Cognitive, subjective and physiological outcomes from modafinil during escalating sleep deprivation. Journal of Sleep Research 13(Suppl. 1), 2004.

Rogers, N.L., Maislin, G., Van Dongen, H.P.A., Dinges, D.F. Neurobehavioural and physiological effects of modafinil during escalating sleep deprivation, Clinical and Experimental Pharmacology and Physiology, 31(s1):A72-A73. 2004.

Dean DA, Mazza MC, Wyatt JK, Czeisler CA, Klerman EB. Circadian and Homeostatic Components of Mathematical Models of Neurobehavioral Performance for the Effects of Low Dose Caffeine During a 42-Hour Forced Desynchrony Protocol. Sleep (Suppl) A77-78, 2004

St. Hilaire MA, Indic PA, Klerman EB, Wright KP, Kronauer RE. Addition of a Non-Photic Component to a Light-Based Mathematical Model of Circadian Rhythms Predicts Entrainment at Low Light Levels. Sleep A71-72, 2004.

2005 (n = 6) Abstracts (includes in press and submitted)

Dean DA, Forger DB, Klerman EB. Designing optimal light intervention schedules for experimental and operational settings. Sleep 28:A69, 2005.

Dean DA, Klerman EB. Using domain specific information to design optimal circadian adjustment schedules. Computation Physiology: from Genome to Physiom Symposium, 35th International Congress of Physiological Sciences. San Diego CA., 2005

Dinges DF, O'Connor R, Van Dongen H. Detecting State Instability: Why PVT Performance Is So Sensitive To Sleep Loss. Sleep 28 (Abstract Supplement): A129, 2005.

Klerman EB, Dean DA II, Gurdziel K, St. Hilaire M, Kronauer RE. Mathematical modeling of human circadian physiology: applications in space and for the general public. IAA Meeting. Graz, Austria, 2005.

Niyogi S, Price NJ, Van Dongen H, Dinges DF. Circulating norepinephrine levels in response to severe sleep deprivation, caffeine, and modafinil. Sleep 28 (Abstract Supplement): A48, 2005.

Rogers, N.L., Maislin, G., Van Dongen, H., Dinges, D.F. Neurobehavioral functioning during 88 hours of sustained wakefulness: Modafinil as a countermeasure. Sleep 28 (Supplement).: A48, 2005.

7. PRESENTATIONS AT SCIENTIFIC MEETINGS, CONFERENCES (N = 182)

Reviews of AFOSR PRET Center Progress by External Scientific Advisory Board.

April 23-24, 2002, Boston, MA (hosted by Harvard University)
March 23-24, 2004 Philadelphia, PA (hosted by University of Pennsylvania)

2000-2005 Presentations (total N = 227)

2000 (n = 3)

DF Dinges: "Assessing neurobehavioral functions in relation to cytokines"—Inflammation, Cytokines & Neurobehavioral Functions Workshop sponsored by Schering, Washington, D.C., October 5, 2000.

DF Dinges: "Effects of Sleep Loss"—Advances in the Treatment of Sleep Disorders, Department of Continuing Education, Harvard Medical School, Cambridge, Massachusetts, October 19, 2000.

DF Dinges: "Can Sleep need be eliminated (or at least reduced) in the new millennium"- Colloquium at the University of Arizona at Tucson, Arizona, November 3, 2000.

2001 (n = 24)

DF Dinges: "Challenges to human behavior and performance during prolonged space flight"--keynote presenter at the National Science Teachers' Association, St. Louis, Missouri, March 27, 2001.

DF Dinges: "Chronically reduced sleep: Do we cope, adapt or deteriorate?" – Science of Mind-Body Interactions: An Exploration of Integrative Mechanisms sponsored by the John D. and Catherine T. MacArthur Foundation Network on Mind-Body Interactions, NIMH, NINDS, and OD OIR NIH, Washington D.C., March 28, 2001.

DF Dinges: "Preventing neurobehavioral deficits from cumulative sleep loss during space flight: Evidence for behavior, pharmacology and technology countermeasures" – invited lecture at Mount Sinai School of Medicine, New York City, New York, May 18, 2001.

DF Dinges: "Sleep debt: Neurobehavioral consequences of chronic partial sleep loss" – invited lecturer at the NIH Behavioral and Social Science Seminar Series, Washington D.C., May 21, 2001.

DF Dinges: "Chronically reduced sleep: Do we cope, adapt or deteriorate?" – invited lecture for the National Advisory Council for Nursing Research, Washington D.C., May 22, 2001.

DF Dinges: "Latest scientific findings/technology approaches" – Air Transport Association Symposium on "Enhancing Aviation Safety", Washington, D.C., May 23, 2001.

DF Dinges: "Sleep Debt: Initial discoveries -- many questions" – The Sixth Annual Trainee Symposium Series at the Association of Professional Sleep Societies 15th Annual meeting in Chicago, Illinois, June 5, 2001.

DF Dinges: "Chronic Sleep Restriction: Relation of Sleep Structure to Daytime Sleepiness and Performance" -Association of Professional Sleep Societies 15th Annual meeting in Chicago, Illinois, June 7, 2001.

DF Dinges: "Human performance and fatigue in modern society" – invited lecture at Groningen Graduate School for Behavioral and Cognitive Neurosciences Summer School in Groningen, Netherlands, July 10, 2001.

DF Dinges: "Performance, fatigue and motivation" -- invited lecture at Groningen graduate School for Behavioral and Cognitive Neurosciences Summer School in Groningen, Netherlands, July 10, 2001.

DF Dinges: "Consequences of acute total sleep deprivation and cumulative partial sleep loss" -- invited lecture at Groningen graduate School for Behavioral and Cognitive Neurosciences Summer School in Groningen, Netherlands, July 11, 2001.

DF Dinges: "The need to identify basic mechanisms of insomnia" –

Neurobiology of Sleep and Waking: Implications for Insomnia Workshop sponsored by National Center on Sleep Disorders Research, National Heart, Lung and Blood Institute, National Institute of Mental Health, National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse in Bethesda, Maryland, September 10, 2001.

DF Dinges: "Cumulative sleep loss in space flight: Neurobehavioral consequences and countermeasures" 52nd International Astronautical Congress in Toulouse, France, October 4, 2001 (canceled due to September 11th attack).

DF Dinges: "Mitigating Fatigue and Maintaining Performance: Risks and Countermeasures" Chest 2001, American College of Chest Physicians in Philadelphia, Pennsylvania, November 8, 2001.

DF Dinges: "The Future of Human Intelligence: Enhancing Cognitive Capability in a 24/7 World" The 3rd International Spearman Seminar in Sydney, Australia, November 30, 2001.

DM Edgar Continuous Assisted Performance Teaming Workshop -- Defense Advanced Projects Research Agency (DARPA) in Las Vegas, NV, August 21-23, 2001.

DM Edgar Bioinformatics in Neuroscience and Sleep Research -- NIH/NHLBI/NCSDR in Bethesda, MD, July 16-17, 2001.

DM Edgar "Waking up to Dopamine," Association of Professional Sleep Societies Annual Meeting, Chicago, IL, 6/2001.

DM Edgar Stimulant-Induced Wakefulness and Sleep Homeostasis. Brown University Sleep Center, E. Providence, RI, January 16, 2001.

DM Edgar Dopamine and Sleep Homeostasis, Dept. Biological Science, Brandeis University, Waltham, MA December 11, 2001.

ME Jewett: Invited Speaker: National Space Biomedical Research Institute, April 2001, Cambridge, MA. "Mathematical models of human circadian rhythms and neurobehavioral performance".

ME Jewett: Invited Speaker: Association of Professional Sleep Societies, June 2001, for Discussion Group "Markers of 'sleep debt' accumulation and recovery: evidence for SWA, REM, TST?".

HPA Van Dongen: "Sleep deprivation and circadian misalignment: Stressors in the 24-hour society" Symposium "Stressor-Induced Alterations in Sleep," Federal University of Sao Paulo, Sao Paulo, Brazil, October 18, 2001.

HPA Van Dongen: "Sleep deprivation in health and disease: Consequences and countermeasures" Colloquium of the Psychiatric Clinic of the University, Tuebingen, Germany, December 19, 2001

2002 (n = 33)

DF Dinges: "Neurobehavioral Functions and Cognitive Performance: Wake Up and Smell the Coffee" The Importance of Sleep for Performance and Health at the Staff Training in Extramural Programs for National Institutes of Health in Bethesda, Maryland, March 28,

2002.

DF Dinges: "Biological versus Social Determinants of Neurobehavioral Capability in a 24/7 World" Fridays @ Four Seminars at the Center for Biological Timing at the University of Virginia, Charlottesville, Virginia, March 29, 2002.

DF Dinges "Causes and consequences of sleepiness: Assessment and intervention" – Philadelphia Division of the American College of Occupational and Environmental Medicine, Philadelphia, PA, 18 September 2002

DF Dinges "Modafinil for the maintenance of performance during sustained operations" – Scientific Update on Provigil Meeting, Scottsdale, AZ, 22 September 2002

DF Dinges "The science of sleep, fatigue and performance" – Association of American Medical Colleges Educational Conference on Resident Physician Duty Hours: Achieving Cultural, Organizational and Operational Change, Chicago, IL, 30 September 2002

DF Dinges "Effects of sleep deprivation" – Advances in Sleep Disorders Medicine, Department of Continuing Education, Harvard Medical School, Cambridge, MA, 17 October 2002

DF Dinges "Research on sleep, fatigue and performance" – Greater General Surgery Grand Rounds, University of Chicago, Chicago, IL, 23 October 2002

DF Dinges: "Sleepiness and fatigue: Neurobehavioral and physiological features" at the American Psychiatric Association 2002 Annual meeting in Philadelphia, Pennsylvania, May 22, 2002.

DF Dinges: "Research on Sleep Fatigue and Performance" Association of American Medical Colleges 2002 Group on Resident Affairs Professional Development Meeting in San Antonio, Texas, April 15, 2002.

DF Dinges: "Napping and fatigue in the workplace" invited speech for the Transport Workers Union of Australia in Melbourne, Australia, July 22, 2002.

DF Dinges: "Napping as a fatigue management tool for drivers in transport industries" invited speech for the Transport Workers Union of Australia in Melbourne, Australia, July 23, 2002.

DF Dinges: "Napping and other solutions for shiftworkers" invited speech for the Transport Workers Union of Australia in Melbourne, Australia, July 23, 2002.

DF Dinges: "Sleep loss and inflammation" invited speech for the Berzelius Symposium 60 in Stockholm, Sweden, August 19, 2002.

DF Dinges: "Manifestations of sleepiness: What does it mean to be awake?" invited keynote address at the Association of Professional Sleep Societies 16th Annual meeting in Seattle, Washington, June 10, 2002.

DF Dinges: "Modafinil improves psychomotor vigilance performance in CPAP-treated obstructive sleep apnea" presented at a poster symposium

at the Association of Professional Sleep Societies 16th Annual meeting in Seattle, Washington, June 10, 2002.

DF Dinges: "New directions for mathematical models of human performance" at the Fatigue and Performance Mathematical Modeling Workshop, Seattle, Washington, June 14, 2002.

DF Dinges: "Manifestations of sleepiness: What does it mean to be awake?" invited lecture at the University of Bergen, Bergen, Norway, May 3, 2002.

DF Dinges: "Sleep and behavioral capability during long duration space flight" invited lecture at the University of Bergen, Bergen, Norway, May 3, 2002.

DM Edgar "Signature profiles in sleep-wake drug discovery," 12th Biannual Congress on Pharmaco-EEG, Barcelona, Spain 22-24 Nov 2002

DM Edgar "Advanced Sleep-Wake Drug Discovery Applications, Primal Inc., Seattle, WA, June 13, 2002.

DM Edgar: "Trainee Day Symposium", Society for Research on Biological Rhythms Meeting, Amelia Island, FL, May 20, 2002

DM Edgar: "Report of progress", AFOSR PRET Center Meeting, Boston, MA, April 23-24, 2002

DM Edgar: "The Great Awakening", article in Washington Post, Washington D.C., June 16, 2002

DM Edgar: "ENU Mutagenesis and High-Throughput Phenotyping in Young Adult Mice", symposium, Associated Professional Sleep Societies Annual Meeting, Seattle WA, June, 2002

DM Edgar: "Alertness Enhancing Therapeutics", Television Interview, CNBC, Washington, D.C., July 2, 2002

ME Jewett: "Performance model simulations of ULR flights: results and recommendations", Crew Alertness in Ultra Long-Range Operations, Paris, France, March 2002.

ME Jewett: Invited Workshop Speaker: Society for Research on Biological Rhythms, May 2002, "Models of light entrainment" for Workshop "Entrainment in humans: what does it take?"

ME Jewett: "Interactive neurobehavioral model", Fatigue and Performance Modeling Workshop, Seattle, WA, June 2002.

NL Rogers: "Sleep deprivation assessment", Clinical Sleep Research Conference, Center for Sleep and Respiratory Neurobiology, University of Pennsylvania, August 24, 2002

NL Rogers: "Neurobehavioural consequences of sleep deprivation, sustained operations and circadian disruption," Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney, Australia, March 18, 2002

HPA Van Dongen: "Chronic sleep restriction" Berzelius Symposium 60 "Sleep as Restitution" by the Swedish Society of Medicine and the Royal Society of Medicine, Stockholm, Sweden, August 20, 2002

HPA Van Dongen: "Comparison of model predictions with experimental data" Fatigue and Performance Modeling Workshop, Seattle, Washington, June

14, 2002.

HPA Van Dongen: "Progress on the study of differential vulnerability to the effects of sleep loss" AFOSR PRET Center Review meeting, Harvard Medical School, Boston, Massachusetts, April 24, 2002.

2003 (n = 55)

CA Czeisler "Effects of Extended Work Hours on ICU Patient Safety" –Plenary Session, AHRQ Annual Patient Safety Conference, Bethesda, MD, 3 March 2003

CA Czeisler: "When Policy Meets Practice: The Challenge of Implementing Change in Resident Work Hours" – 2003 American Council of Graduate Medical Education Annual Education Conference, Chicago, IL, 6 March 2003

CA Czeisler "Role of Shift Work (Especially Night Work) in Sleep Disorders and Cardiovascular Risks" NHLBI & NINDS Workshop on Effects of Sleep Disorders and Sleep Restriction on Adherence to Cardiovascular & Other Disease Treatment Regimens, Bethesda, MD, March 11, 2003.

CA Czeisler "Resetting Circadian Clocks in Humans" Gordon Research Conference: Chronobiology II Ciocco, Luca, Italy, May 11, 2003.

CA Czeisler "Sleep, Biological Clocks and Health" Harvard Alumni Association Alumni College, Cambridge, MA, May 18, 2003.

CA Czeisler "Exploring Issues Related to Circadian Rhythm Misalignment" APSS Conference, Chicago, IL, May 27, 2003.

CA Czeisler "Photic resetting of the human circadian pacemaker" Chautauqua Circadian Biology, Harvard University, Cambridge, MA, May 30, 2003.

CA Czeisler "Briefing on Harvard Study of Physician Work Hours and Patient Safety" British Medical Association, London, UK, June 12, 2003.

CA Czeisler "Physiologic Determinants of Alertness and Performance: Implications for Physician Work Hours, Safety & Learning" Partners Faculty Development Conference, Massachusetts General Hospital, Boston, MA, June 16, 2003.

CA Czeisler: "Effect of Sleep Deprivation and Biological Time of Day on Human Performance" – Spaulding Distinguished Lecture, Spaulding Hospital, Boston, MA, 20 June 2003

CA Czeisler "Circadian and Homeostatic Regulation of Sleep and Wake" MPM Capital Medical Scientific Advisory Board Retreat, Goat Island, Newport, RI, August 7, 2003.

CA Czeisler "Properties of the Human Circadian Pacemaker" Berlin School on Circadian Rhythms Charité Hospital, Humboldt University, Berlin, October 13, 2003.

CA Czeisler "Properties of Human Circadian Pacemaker, II: Intrinsic period and entrainment" Berlin School, Berlin, October 16, 2003

CA Czeisler "Physiologic Determinants of Alertness and Performance: Implications for Physician Work Hours, Safety & Learning" Briefing

for MICU Attending Physicians, Brigham and Women's Hospital, Boston, MA, October 17, 2003.

CA Czeisler "Effects of Extended Work Hours on Performance in the ICU" AMSUS, November 18, 2003.

CA Czeisler "Circadian Clocks and Human Sleep" Institute for Systems Biology, Seattle, WA, November 19, 2003.

CA Czeisler "Circadian Disorders: Update 2003" Medical Advisory Council, Respironics, Inc., Philadelphia, PA, December 3, 2003.

DF Dinges "Sleep and circadian control of neurobehavioral functions" University of Pennsylvania Center for Cognitive Neuroscience Seminar Series Philadelphia, PA, October 20, 2003.

DF Dinges "Nutrition effects on sleep deprivation" – Mars Nutrition Research Council, Miami, FL, 24 January 2003

DF Dinges "Sleepiness and fatigue: Impact on performance" – Mayo Clinic, Rochester, MN, 10 February 2003

DF Dinges "Sleep deprivation and fatigue and its effect on performance—The science and its implications for resident duty hours" – Accreditation Council for Graduate Medical Education's March 2003 "Mastering the Accreditation Process" Meeting, Chicago, IL, 6 March 2003

DF Dinges "The science of sleep, fatigue and performance: Implications for resident duty hours." Grand Rounds, Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, September 23, 2003.

DF Dinges "Sleep deprivation, fatigue and effects on performance." Medical Education Grand Rounds, Southern Illinois University School of Medicine, Springfield, IL, September 29, 2003.

DF Dinges "Monitoring fatigue and performance: Implications for resident duty hours." Association of American Medical Colleges Educational Conference. "Resident Physician Duty Hours: Implementing the New Requirements." Chicago, IL, September 29, 2003.

DF Dinges "The effect of sleep deprivation on performance" Continuing education program Johns Hopkins University School of Medicine Division of Pulmonary and Critical Care Medicine Baltimore, MD, October 4, 2003.

DF Dinges "Sleep deprivation in physicians and trainees" Medical Grand Rounds Drexel University College of Medicine, Hahnemann University Hospital Philadelphia, PA, October 8, 2003.

DF Dinges "The Science of Sleep, Fatigue and Performance" – Continuing Medical Education Program of the Froedtert Memorial Lutheran Hospital, Milwaukee, WI, 2 April 2003

DF Dinges "Modern Humans and Sleep Deprivation" – The American Philosophical Society's Annual General Meeting, Philadelphia, PA, 24 April 2003

DF Dinges	"Attending Cardiothoracic Surgeon Should Also Be Subject to Work-Hour Regulations" – Annual Meeting of the American Association for Thoracic Surgery, Boston, MA, 7 May 2003
DF Dinges	"Neurobehavioral and Cognitive Effects of Sleep loss: Theory and Measurement" – 17th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL, 3 June 2003
DF Dinges	"Sleep Restriction" – 17th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL, 4 June 2003
DF Dinges	"Sleep Deprivation and Simulator Research" – 17th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL, 4 June 2003
DF Dinges	"Subjective Sleepiness in Acute and Chronic Sleep Loss" – 17th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL, 6 June 2003
DF Dinges	"State instability, neurobehavioral function and sleep homeostasis in sleep-deprived humans" 2003-04 Current Issues in Neuroscience and Behavior Seminar, Princeton University Princeton, NJ, October 23, 2003.
DF Dinges	"Dose-response effects of chronic sleep restriction in healthy adults" Non-restorative Sleep, The Stanford Sleep Epidemiology Research Center, Stanford University Palo Alto, CA, December 8, 2003.
DM Edgar	"Transitioning basic science into the clinic" – Grand Rounds, Sleep Disorders Research Center, Stanford University, 7 March 2003
DM Edgar	Keynote Lecture, "Sleep-wake therapeutics and the future of healthcare" – Forward Ventures Limited Partners Annual Meeting, San Diego, CA 18 March 2003
DM Edgar	"Trainee Day", Associated Professional Sleep Societies, Chicago, 4 June 2003
DM Edgar	MPM Capital Biotechnology Retreat, Bermuda, 16-18 June 2003
DM Edgar	"Discovering wake promoting therapeutics" – MPM Capital Medical and Scientific Advisory Board, Newport Beach, RI, 6-8 August 2003
DM Edgar	"Somnolytic wake-promoting therapeutics" – DARPA/DSO, 19 August 2003
DM Edgar	"Wake-promoting therapeutics" – Halberg Chronobiology Center, University of Minnesota, MN, 20 August 2003
EB Klerman	Invited discussion group participant in Discussion group "Sleep need and compensatory response to sleep loss: can these factors be defined for individuals?" APSS annual meeting 2003. Chicago IL.
NJ Price	"Recovery from total sleep deprivation" – Clinical Sleep Research Conference of the Center for Sleep and Respiratory Neurobiology, University of Pennsylvania, Philadelphia, 26 August 2003
NL Rogers	"Sleep Loss – Consequences for Human Performance, Sleep Loss: Risks and Solutions in the Workplace Symposium" Sydney, NSW, Australia, 13 October 2003

NL Rogers	"Chronic sleep restriction: Neurobehavioral and endocrine effects" – Associated Professional Sleep Societies. Continuing Medical Education Course—The Effect of Sleep Loss and Sleep Restriction in Humans. Chicago, IL, 3 June 2003
NL Rogers	"Pharmaceutical Countermeasures to Sleep Loss, Sleep Loss: Risks and Solutions in the Workplace Symposium" Sydney, NSW, Australia, 13 October 2003
NL Rogers	"Sleep Loss and General Health, Sleep Loss: Risks and Solutions in the Workplace Symposium" Sydney, NSW, Australia, 13 October 2003
HP Van Dongen	"Sleep loss, neurobehavioral performance and psychological factors" International Workshop "Facets of Wakefulness and Sleepiness: Causes, Consequences, and Assessment," Ascona, Switzerland, March 5, 2002
HP Van Dongen	"Current biomathematical models of temporal changes in human fatigue and performance" – Seminar of the Human Factors Research Technology Division, NASA Ames Research Center, Moffett Field, California, 7 August 2003
HP Van Dongen	"Fatigue and safety: Chronic sleep loss, wake state instability, and inter-individual differences" – Truck Driver Occupational Safety and Health Conference, Wayne State University, Detroit, 25 April 2003
HP Van Dongen	"The neurobehavioral price for wakefulness" – Sleep Lecture Series of the Center for Sleep and Respiratory Neurobiology, University of Pennsylvania, Philadelphia, 13 March 2003
KP Wright	"Integrative Research on the Physiology of Sleepiness and Fatigue: Observations of a Sleep and Clock Watcher" – Center for the Integrative Study of Work. University of Colorado, Boulder CO, 2003
KP Wright	"Photic entrainment of the human circadian timing system to the day length of Mars" – American Society for Photobiology, Baltimore, MD, 2003
KP Wright	"Control of Waking Functions by Homeostatic and Circadian Processes" – Associated Professional Sleep Societies. Continuing Medical Education Course—The Effect of Sleep Loss and Sleep Restriction in Humans. Chicago, IL, 3 June 2003

2004 (n = 75)

CA Czeisler	Human Performance Factors, Sleep and Chronobiology Team Presentation, National Space Biomedical Research Institute, Houston, TX, January 15, 2004.
CA Czeisler	"Sleep 101: Sleep, Drive, Circadian Rhythms and Energy." International Life Sciences Institute Scientific Session on Sleep, Energy and Health, Washington, D.C., January 19, 2004.
CA Czeisler	"Circadian rhythms, sleep and waking performance" Vanda Pharmaceuticals, Rockville, MD, March 3, 2004.

CA Czeisler	HMS Division on Aging CME Course "Sleep and Aging," Boston, MA, March 4, 2004.
CA Czeisler	"Determinants and Characteristics of Healthy Sleep: Maintaining Physiologic Homeostasis" Frontiers of Knowledge in Sleep & Sleep Disorders, National Sleep Conference, NCSDR, NHLBI, Trans-NIH SRCC, Bethesda, MD, March 29, 2004.
CA Czeisler	"Circadian Nature of Humans: Sleep, Mood and Cognition" Aventis AVE9782 Scientific Advisory Board, Short Hills, New Jersey, April 9, 2004.
CA Czeisler	"Sleep, circadian rhythms and waking performance" Bose Corporation, Framingham, MA, April 29, 2004.
CA Czeisler	"Neurobiology of Human Sleep and Circadian Rhythms: Implications for Physician Work Hours." Medical Grand Rounds, Tufts-New England Medical Center, Boston, MA, May 28, 2004.
CA Czeisler	"Circadian Determinants of Alertness: Are they Altered in Sleep Disorders?" 2nd International Sleep Disorders Forum sponsored by Sanofi Synthelabo, Paris, France, September 10, 2004.
CA Czeisler	"The Fatigued Internist" Bioterrorism and Trauma Conference, University of Maryland, Baltimore, MD, September, 22, 2004.
CA Czeisler	"Physiological and Behavioral Determinants of Healthy Sleep and Waking: Interaction of Circadian and Homeostatic Processes." Neurocrine, San Diego, San Diego, CA, October 22, 2004.
CA Czeisler	Medical Grand Rounds: Brigham and Women's Hospital "Extended Work Shifts, Motor Vehicle Crashes and Serious Medical Errors" Department of Medicine, Brigham and Women's Hospital, Boston, MA, October 15, 2004.
CA Czeisler	"Fatigue and Error" The Patient Safety Imperative, Boston, MA, October 25, 2004.
CA Czeisler	"How do circadian rhythms affect sleep (wake) in humans?" Unilever, United Kingdom, November 1, 2004.
CA Czeisler	"A novel approach to enhancing alertness with caffeine" Unilever, United Kingdom, November 2, 2004.
CA Czeisler	Current State of Critical Care Lecture Series "Extended Work Shifts, Motor Vehicle Crashes and Serious Medical Errors" Department of Medicine, Brigham and Women's Hospital, Boston, MA, November 4, 2004.
CA Czeisler	West Roxbury VA Hospital Seminar Series, "Extended Work Shifts and Medical Errors of Interns" West Roxbury, MA, December 9, 2004.
CA Czeisler	"Extended Work Shifts, Motor Vehicle Crashes and Work Errors" National Association of Police Organizations Headquarters, Washington, D.C., December 10, 2004.
DA Dean	"Circadian and Homeostatic Components of Mathematical Models of Neurobehavioral Performance for the Effects of Low Dose Caffeine During a 42-Hour Forced Desynchrony Protocol." APSS annual meeting. Philadelphia. June 2004.

DF Dinges "Sleep, energy, and alertness" International Life Sciences Institute's Annual Meeting 2004 North America Scientific Session on Sleep, Energy, and Health Washington, DC, January 19, 2004.

DF Dinges "The science of sleep, fatigue and performance" Medical Grand Rounds Beth Israel Medical Center, New York City, New York, March 2, 2004.

DF Dinges "Overview of sleep/wake homeostasis: Relation to shift work" National Sleep Foundation's Workshop on Shift Work Sleep Disorder in Washington DC, March 4, 2004.

DF Dinges "Performance and alertness" National Transportation Safety Board Academy Course Investigating Human Fatigue Factors in Transportation Accidents, Ashburn, VA, March 10, 2004.

DF Dinges "Scheduling Factors" National Transportation Safety Board Course Investigating Human Fatigue Factors in Transportation Accidents in Ashburn, VA, March 10, 2004.

DF Dinges "Performance (Accidents, Drowsy Driving)" Frontiers of Knowledge in Sleep & Sleep Disorders: Opportunities for improving Health and Quality of Life sponsored by National Center on Sleep Disorders Research, National Heart, Lung and Blood Institute and Trans-NIH Sleep Research Coordinating Committee, NIH, Bethesda, MD, March 29, 2004.

DF Dinges "Sleep and circadian control of neurobehavioral functions in a 24/7 world" Grand Rounds, University of California San Diego Medical Center, San Diego, CA, April 1, 2004.

DF Dinges "Sleep deprivation: Monitoring fatigue and performance" Grand Rounds, The Lankenau Hospital, Wynnewood, PA, April 7, 2004.

DF Dinges "The science of fatigue effects on performance" Grand Rounds, Sinai Hospital, Baltimore, MD, April 8, 2004.

DF Dinges "Studies of human sleep deprivation and neurobehavioral functioning" Fatigue and Performance Modeling Partnerships at the Walter Reed Army Institute for Research, Silver Spring, MD, April 14, 2004.

DF Dinges "Sleep Deprivation, fatigue and performance – the science and its implications for resident duty hours" The Carabasi Lectureship, Scott & White Memorial Hospital, Temple, TX, April 23, 2004.

DF Dinges "Managing sleep need, circadian phase, and human performance; Professionalism in a 24-7 environment" American Association for Thoracic Surgery 84th Annual Meeting, Toronto, Canada, April 24, 2004.

DF Dinges "The neurobiology of fatigue and performance" Association of American Medical Colleges, Council of Deans Spring Meeting, Key Biscayne, FL, April 27, 2004.

DF Dinges "Ensuring human behavioral capability at the frontiers of space and time" The 39th Harry G. Armstrong Lecture at the 75th Annual Aviation Space Medicine Association meeting, Anchorage, Alaska, May 6, 2004.

DF Dinges "The criticality of sleep for health and safety in a 24/7 world" The Decade of Behavior Award, Washington DC, May 10, 2004.

DF Dinges "Science of sleep, fatigue and performance: Implications for the resident duty hours" Vukov Lecture, Oregon Health & Science University, Portland, Oregon, May 13, 2004.

DF Dinges "State instability and the neurocognitive effects of sleep loss" SCOR Symposium, Boston, Massachusetts, May 17, 2004.

DF Dinges "Review of scientific literature on the impact of circadian changes, sleep disorders and experimental sleep deprivation/restriction on neurocognitive and affective functioning" 18th Annual Meeting of the Associated Professional Sleep Societies, Philadelphia, Pennsylvania, June 6, 2004.

DF Dinges "Sleepiness and performance" 18th Annual Meeting of the Associated Professional Sleep Societies, Philadelphia, Pennsylvania, June 8, 2004.

DF Dinges "Testing theoretical predictions on the neurobehavioral effects of sleep loss in humans" 18th Annual Meeting of the Associated Professional Sleep Societies, Philadelphia, Pennsylvania, June 10, 2004.

DF Dinges "Why we sleep: Sleep and performance" Connecticut Neurological Society Meeting, Farmington, Connecticut, June 18, 2004.

DF Dinges "Do we have proper tools to measure impaired alertness?" The Art of Good Sleep Meeting, Paris, France, September 10, 2004.

DF Dinges "Science of sleep, fatigue and performance" Grand Rounds, The Children's Hospital of Philadelphia, Philadelphia, PA, September 15, 2004.

DF Dinges "Cognitive, subjective and physiological outcomes from Modafinil during escalating sleep deprivation" 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 6, 2004.

DF Dinges "What is sleep debt?" 17th Congress of the European Sleep Research Society, Prague, Czech Republic, October 7, 2004.

DF Dinges "Vigilance in a 24/7 world: I. Sleep need and circadian rhythms" Massachusetts Society of Anesthesiologists, Southampton, Bermuda October 11, 2004.

DF Dinges "Vigilance in a 24/7 world: II. Countermeasures for fatigue" Massachusetts Society of Anesthesiologists, Southampton, Bermuda, October 11, 2004.

DF Dinges "Effects of fatigue on cognitive performance and X-ray target detection" Transportation Security Administration Meeting in Atlantic City, NJ, October 21, 2004.

DF Dinges "Reaction time and psychomotor function" Johnson Space Center Cognitive Meeting, Phoenix, AZ, October 25, 2004.

DF Dinges "Consequences of chronic insufficient sleep" Grand Rounds, Emory University School of Medicine, Atlanta, GA, October 27, 2004.

DF Dinges	"Monitoring fatigue and performance: Implications for resident duty hours" Emory University School of Medicine, Residency Education, Atlanta, GA, October 27, 2004.
DF Dinges	"Real world consequences of sleep and circadian disorders" Sleep Medicine Lecture Series, Royal Prince Alfred Hospital, Camperdown NSW, Australia, November 16, 2004.
DF Dinges	"Lessons from Exxon Valdez and other disastors: Have we underestimated the consequences of sleep loss?" 2nd Annual Symposium on Sleep Loss, Eveleigh NSW, Australia, November 17, 2004.
DF Dinges	"Reducing the risk—the prevent, detect and intervene approach to sleep loss and shift work—naps, hours of work and pharmacological approaches", 2nd Annual Symposium on Sleep Loss, Eveleigh NSW, Australia, November 17, 2004.
DF Dinges	"Can computer models predict fatigue?" 2nd Annual Symposium on Sleep Loss, Eveleigh NSW, Australia, November 17, 2004.
DF Dinges	"Sleep loss and its neurocognitive consequences" Neurology Grand Rounds, Northwestern University, Chicago, IL, November 30, 2004.
DF Dinges	"Science of Sleep & Performance: Relevance to Residency Duty Hours" Division of Urology Grand Rounds, University of Pennsylvania Health System, Philadelphia, PA, December 9, 2004.
DM Edgar	"Accelerating preclinical assessment of sleep-wake drug candidates" Preclinical Development Forum, Cambridge, MA, Feb 23, 2004.
DM Edgar	"Accelerating preclinical assessment of sleep-wake drug candidates" Preclinical Development Forum, Cambridge, MA, Feb 23, 2004.
DM Edgar	"Wakefulness-Promoting Therapeutics and Sleep Homeostasis", Grand Rounds, Dept. Neurology, Emory University, Host: Dr. David Rye, December 16, 2004.
DM Edgar	"Accelerating preclinical assessment of sleep-wake drug candidates." Preclinical Development Forum, Cambridge, MA Feb 23, 2004.
DM Edgar	"Advances in Sleep-Wake Drug Discovery," Halberg Chronobiology Center, University of Minnesota Medical Center, Minneapolis, August 20, 2003.
DM Edgar	"Somnolytic wake-promoting therapeutics" – DARPA/DSO, 19 August 2003
DM Edgar	"Discovering wake promoting therapeutics," MPM Capital Medical & Scientific Advisory Board Meeting, Newport, RI, August 6-8, 2003
DM Edgar	MPM Capital Biotechnology Retreat, Bermuda, 16-18 June 2003.
DM Edgar	"Trainee Day", Associated Professional Sleep Societies, Chicago, 4 June 2003.
DM Edgar	" Novel Pharmaceuticals for Treating Sleep Disorders." 5th Annual C21 Ventures Conference, May 28-30, 2003.

DM Edgar	Keynote Lecture, "Developing Novel Pharmaceuticals for the Vast Terrain of Sleep Disorders," Forward Ventures Limited Partners Annual Meeting, San Diego, March 18, 2003.
DM Edgar	"Transitioning Basic Science into the Clinic," Grand Rounds, Sleep Disorders Clinic and Research Center, Stanford University, March 7, 2003.
EB Klerman	"Modeling circadian and sleep biology - implications for astronaut performance" Weekly CME conference, NASA Houston TX March 2004.
EB Klerman	"Modeling circadian and sleep biology - implications for astronaut performance" Weekly CME conference, NASA Houston TX March 2004.
EB Klerman	"Mathematical modeling of neurobehavioral performance"AFOSR PRET Center Review Philadelphia, PA 2004
EB Klerman	Association of Professional Sleep Societies, Philadelphia, PA Invited discussion group participant. Discussion group title: "Current Concepts and Models of Response to Sleep Loss" 2004 Philadelphia.
EB Klerman	Society for Research in Biological Rhythms. Whistler Canada 2004. Symposium chair "Clinical Implications of Clock function"
NL Rogers	"Countermeasures to neurobehavioral deficits from chronic partial sleep deprivation during space flight" NSBRI symposium, Society for Research on Biological Rhythms meeting, Whistler, BC, Canada, 23 June 2004
NL Rogers	"Management of sleep problems in jet lag and shift work" in Asthma, COPD, Respiratory & Sleep Disorders Update and Education Day, Randwick, NSW, Australia, 24 July 2004

2005 (n = 37)

CA Czeisler	Human Performance Factors, Sleep and Chronobiology Team Presentation, National Space Biomedical Research Institute, Houston, TX, January 11, 2005.
CA Czeisler	"Harvard Work Hours, Health and Safety Study: Impact of Extended Duration Work Shifts on Patient and Intern Safety" Safety and ICU Shift Duration 34th Critical Care Congress, Phoenix, AZ, January 17, 2005.
CA Czeisler	"Improving Safety and Health of Massachusetts State Police: Operation Healthy Sleep" State Police Meeting, State Police Headquarters, Framingham, MA, January 28, 2005.
CA Czeisler	"Sleep-Wake Actigraphy and Light Exposure During Spaceflight" Bioastronautics Workshop, National Aeronautics and Space Administration, Johnson's Space Center, Houston, TX, February, 2005.
CA Czeisler	"Assessing Circadian Rhythms and Their Interactions with Sleep" Sleep Research Society Course, Miami, FL, February 4, 2005.

CA Czeisler "Sleep and Aging" HMS Division on Aging CME Course, Four Seasons Hotel, Boston, MA, March 4, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours in the US Medical Community" Fatigue, Sleep and Biological Clocks International Conference, Linbury Trust Centre for Chronobiology, Imperial College London and University of Surrey, London, UK, March 31, 2005.

CA Czeisler "Comprehensive Fatigue Management Program" Impact of Work Hours on Police Officer Health & Safety: A nationwide evaluation by the Harvard Work Hours, Health and Safety Group, Fraternal Order of Police, Lodge 3, Baltimore City Police Department, Baltimore, MD, April 16, 2005.

CA Czeisler "Sleep Dynamics: REM, Rhythms & Recall" Longwood Seminar, Harvard Medical School, April 27, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Impact of Extended Duration Work Shifts on Patient and Intern Safety" Anesthesia Grand Rounds, Brigham and Women's Hospital, Boston, MA, May 4, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours in the US Medical Community" Chautauqua Circadian Biology Course, Harvard University, May 13, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours in the US Medical Community" Institute for Experimental Psychiatry Board of Trustees Meeting, Harvard Club, Boston, MA, May 17, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours in the US Medical community" Keynote Address, Committee of Interns and Residents, 2005 National Convention, Washington, D.C., May 21, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours in the US Medical Community" Plenary Lecture, Society of Neurological Surgeons Annual Meeting Stanford, CA, May 24, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation and Work Hours: Impact on Intern and Patient Safety" House Staff Orientation, Brigham and Women's Hospital, Boston, MA, June 16, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Sleep Deprivation in Residency in Training" SRS Trainee Symposium, Denver CO, June 19, 2005.

CA Czeisler "Sustaining Wakefulness in Excessive Sleepiness Consequence Prevention" APSS Meeting, Denver CO, June 19, 2005.

CA Czeisler "Harvard Work Hours, Health and Safety Study: Impact of Extended Duration Work Shifts on Patient and Intern Safety" Safety and ICU Shift Duration, Royal College of Surgeons European Working Time

	Directive Task Group Meeting, London, United Kingdom, August 10, 2005.
DF Dinges	"Fatigue management technologies" Federal Motor Carrier Safety Administration Office of Research and Technology Fifth Annual Forum, Washington, DC, January 9, 2005.
DF Dinges	"The critical need for sleep" Veterans Affairs Medical Center, Philadelphia, PA, January 19, 2005.
DF Dinges	"The hectic life" North American Branch of the International Life Sciences Institute's Workshop on Sleep and Quality of Life, Washington, DC, February 16, 2005.
DF Dinges	"Human sleep duration and risk: What do we think we know?" Sleep Lecture Series, Sleep Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA , March 9, 2005.
DF Dinges	"Sleep and circadian control of neurobehavioral functions" Seminar Series Neuroscience and Cognitive Sciences Program at the University of Maryland, College Park, MD, March 18, 2005.
DF Dinges	"Human performance, capability and behavior" Transportation Research Board Conference on Future Truck and Bus Safety Research Opportunities, Washington, DC, March 23, 2005.
DF Dinges	"Neurobehavioral risks of sleepiness: Modafinil as a counter measure" Fatigue, Sleep and Biological Clocks International Conference at the Imperial College, London, England, April 1, 2005.
DF Dinges	"Sleep Duration: Neurobehavioral, Physiological and Epidemiological Issues" IOM Committee on Sleep Research and Sleep Medicine Workshop on the Pubic Health Significance of Sleep Deprivation and Disorders, The National Academies, Washington, DC, April 12, 2005.
DF Dinges	"Biological Limits to Performance During Extended Duty Days: Work Time, Wake Time, Rest Time, Sleep Time, Clock Time, Biological Time" In: ULR—Extending the Duty Day: Effects on the Operational Performance of Commercial Aviators, 76th Annual Aviation Space Medicine Association meeting, Kansas City, MO, May 10, 2005.
DM Edgar	"Improving chemical scaffolds to treat sleep-wake disorders", CBI Drug Repurposing Conference, Philadelphia, PA, February 1, 2005.
DM Edgar	Mathematical Modeling Applications in the Life Sciences, DARPA Workshop, Arlington, VA, January 7, 2005.
DM Edgar	"Hunting for pharmacological targets to promote wakefulness", Beth Israel Medical Center, Dept. Neurology, Harvard University, Host: Drs. Clifford Saper and Thomas Scammell, January 20, 2005.
EB Klerman	NASA Bioastronautics Workshop, Invited presenter of abstract "Mathematical models of circadian/performance countermeasures"2005.

EB Klerman	Radcliffe Institute for Advanced Study at Harvard University seminar, Invited presenter at "Mechanisms of Seasonality in Directly Transmitted Infectious Diseases" 2005.
EB Klerman	Mathematical modeling of human circadian physiology: applications in space and for the general public. IAA Meeting. 2005. Graz, Austria. 2005
EB Klerman	Association of Professional Sleep Societies, Denver, CO, Invited discussion group participant. Discussion group title: "Measuring Melatonin in Humans: Reliability Issues and Important Factors That Need to be Controlled" 2005
EB Klerman	Association of Professional Sleep Societies, Denver, CO, Session chair "Circadian rhythms: 2005
EB Klerman	Gordon Research Conference on Chronobiology. Session Co-Chair/Discussion leader "Output signals and peripheral clocks: 2005
NL Rogers	Neurobehavioral functioning during 88 hours of sustained wakefulness: Modafinil as a countermeasure. Presented at Neuroscience-From bench to bedside, University of Sydney, Sydney, Australia, 2005.

Trade Journals

DM Edgar	Hypnion: Laying an old problem to rest. Bioventure View 19(7/8): 23, 2004.
DM Edgar	The 100 Most Influential Companies. Acumen Journal of Life Sciences 11(2): pg 55, 2004.

Mass Media / Popular Press

DM Edgar	Washington Post "The Great Awakening" June 17, 2002.
DM Edgar	CNBC, Capital Report, Wake Promoting Therapeutics, July 2, 2002
DM Edgar	BioCentury, "Hypnotizing insomniac investors, March 24, 2003. 2002.
DM Edgar	Boston Globe "Bucking the Trend", May 12, 2003.
DM Edgar	Wall Street Journal, The Quest to Banish Fatigue, 1 July 2003
DM Edgar	Worcester Telegram and Gazette, Focused on Sleep, 13 July 2003
DM Edgar	Wired Magazine, feature article "It's Wake-Up Time," pp. 138-141, November 2003
DM Edgar	Reader's Digest, feature article "Less Sleep, More Energy," pp. 102-107, October 2004

8. CONSULTATIVE / ADVISORY TO OTHER LABORATORIES/AGENCIES

2000-2005 chronological (Total N = 28)

L Barger:	Consultant to Col. Peter F. Demitry M.D. of the Air Combat Command (ACC) on fatigue countermeasures

CA Czeisler:	Advisor to Cephalon, Inc. and the FDA regarding the assessment of the effects of modafinil.
CA Czeisler	Member, Medical and Scientific Advisory Board, Hypnion, Inc., Lexington, MA
CA Czeisler	Consultant, Respironics, Inc., Murrysville, PA
CA Czeisler	Consultant, Vanda Pharmaceuticals, Inc., Rockville, MD
CA Czeisler:	Advisor to Cephalon, Inc. and the FDA regarding the assessment of the effects of modafinil, 2000-2005
DF Dinges:	Advisor to Cephalon, Inc. and the FDA regarding the assessment of the effects of modafinil, 2000-2005
DM Edgar:	NIH research advisor to Prof. E. Mignot at Stanford University, August 2000-2005
DM Edgar:	Continuous Assisted Performance Teaming Workshop Defense Advanced Projects Research Agency (DARPA), August 2001
NL Rogers:	Consultant on stimulant use during missions, United States Air Force, 2001-2004
NL Rogers:	Consultant to Col. P. Dimitry, AFOSR/NL, AFOSR PRET Center Research Compendium of Products. August – October, 2000.
NJ Price:	Consultant to Col. P. Dimitry, AFOSR/NL, AFOSR PRET Center Research Compendium of Products. August – October, 2000.
DF Dinges:	Consultant to Col. P. Dimitry, AFOSR/NL, AFOSR PRET Center Research Compendium of Products. August – October, 2000.
KP Wright, Jr.:	Consultant to "Mars Exploration Rover Surface Operations Human Factors Workshop". Promoting Wakefulness Through Sleep Management and Circadian Rhythm Adjustment. NASA Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California. January 2001.
CA Czeisler:	Consultant to "Mars Exploration Rover Surface Operations Human Factors Workshop". Promoting Wakefulness Through Sleep Management and Circadian Rhythm Adjustment. NASA Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California. January 2001.
DF Dinges:	Chair, Organizing Committee, "Neurobiology of Insomnia" Workshop, National Institutes of Health, Bethesda, MD, September 2001.
DF Dinges:	Member, Organizing Committee, "Sleep and Fatigue in Medical Training" Workshop, NIH, AMA, AASM, SRS, AHRQ, Arlington, VA, October 2001.
DF Dinges:	Member, Organizing Committee, "Math Modeling" Workshop, Seattle, WA, June, 2002
DM Edgar:	IFCN-5 Study Section Member of DRG, National Institutes of Health, February 2002, March 2003
DM Edgar:	Presentation and cooperative discussions to QuinitiQ, UK, Farnborough, UK, June 27, 2002
NL Rogers:	Member of NASA and the University of Missouri – Columbia sponsored workshop on: Sex, Space, and Environmental

	Adaptation: A National Workshop to Define Research Priorities Regarding Sex Differences in Human Responses to Challenging Environments (Congressionally mandated workshop), 2002
HP Van Dongen:	Member, Organizing Committee, "Math Modeling" Workshop, Seattle, WA, June, 2002
DM Edgar:	IFCN-5 Study Section Member, National Institutes of Health, Bethesda, MD, March, 2003.
NL Rogers:	Consultant on Sleep loss and Circadian Rhythm Disruption, Sanofi-Synthelabo (U.S.)/ R U Fit, 2003-2004
DM Edgar:	Research advisor and consultant to Prof. Emmanuel Mignot, Center for Narcolepsy, Stanford University School of Medicine.
L Barger:	Consultant to Col. Peter F. Demitry M.D. of the Air Combat Command (ACC) on fatigue countermeasures
ME Jewett:	Consultant to Chris Flynn, M.D., NASA Flight Surgeon at Johnson Space Center, further developing the performance model software to incorporate sleep/wake and light exposure data collected in space with actigraphy to predict performance of astronauts on Space Shuttle missions.
DA Dean II:	Consultant to Math Works, Natick MA, the company that produces the modeling software called MatLab. In this collaboration, Mr. Dean has been able to beta test the company's newest software tools and advise them as to how the tools could be changed so that they would be best applied to our modeling needs.

Note: PRET Center investigators and industry partners also had a large number of advisory and consultative communications via e-mail, telephone, fax, and in writing, as well as meetings specifically focused on methodological and technical aspects of the projects.

9. TRANSITIONS

2000-2005 – Data from the experiments at the University of Pennsylvania and Harvard University have been incorporated into biomathematical and computational models of alertness and performance currently being developed to counteract fatigue associated with Air Force missions.

2000-2001 – Dr. Edgar was involved in the transfer of SCORE-2000™ Sleep-Wake Bioassay Technology to Hypnion Inc. (www.Hypnion.com), under an exclusive corporate licensing agreement with Stanford University. Hypnion is a sleep-wake biotechnology company co-founded by Dr. Edgar. This technology transfer was contractually initiated in August of 2000 and was fully completed in 2001. Application: Commercial screening of drugs for sleep-wake effects and/or side effects and forward genetics-based novel drug target discovery program. Hypnion also has in-licensing efforts to identify novel safe & effective soporific drugs and wake promoting therapeutics for maintaining alertness.

2000-2001 - Dr. Edgar was involved in the transfer of his discovery research innovations in the area of insomnia and wake-promoting therapeutics, including his SCORE-2000™ Sleep-Wake Pharmacology Database Pharmacological Standards Archives to Hypnion Inc. This technology transfer was contractually initiated in August of 2000 and was fully completed in 2001, and it benefited Oxford Bioscience Partners, Flagship Ventures, GIMV, MPM Capital, Forward Ventures, Advanced Technology Ventures, Founders and Board of Directors of Hypnion, Inc. Application: Commercial development (discovery medicinal chemistry, pharmacology, toxicology and clinical) of novel chemical entities designed to treat sleep maintenance insomnia (including battlefield and operations-related insomnia), to reduce the latency to return to sleep in insomnia and jet-lag, and to treat inappropriate sleepiness and associated cognitive decline associated with jet-lag, shift-work and sustained operations.

2002-2004 – Drs. Dinges and Van Dongen were co-organizers of the "Math Modeling" Workshop held in Seattle, WA, in June 2002 that was jointly funded by the AFOSR and NASA. A number of members of the AFOSR PRET Center were involved and made presentations during this meeting, including Drs Dinges, Van Dongen, Czeisler and Jewett. A summary of this meeting was published in a special edition of the journal Aviation, Space & Environmental Medicine in 2004. The data from PRET Center experiments conducted by Dr. Dinges were used extensively as a platform for evaluating mathematical models.

2002-2005 – Dr. Dinges was asked by The Accreditation Council for Graduate Medical Education (ACGME) to assist in educating physicians and surgeons on the adverse effects of sleep deprivation and night work on performance. ACGME is responsible for the accreditation of post-MD medical training programs within the United States. Accreditation is accomplished through a peer review process and is based upon established standards and guidelines. Dr. Dinges spoke on these issues at the annual meetings of ACGME and the Association of American Medical Colleges (AAMC), as well as giving grand rounds at more than 30 major medical training programs (including NIH, Mayo, University of Chicago, New York University, etc.). Data and knowledge acquired through AFOSR PRET Center research figured prominently in his presentations on the effects of fatigue and its mitigation by countermeasures.

2000-2005 – Based on the encouraging data that we gathered from the PRET, Drs. Czeisler and Dinges advised Cephalon, Inc., which produces modafinil, on the potential use of modafinil in the treatment of Shift Work Sleep Disorder. They carried out a pilot protocol and designed a multi-center clinical trial. The results of that trial—the first evaluation for a treatment for that underrecognized condition--have just been published in the New England Journal of Medicine (Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, Kingsbury L, Arora S, Schwartz JR, Niebler GE, Dinges DF; U.S. Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. N Engl J Med. 2005;353:476-486.)

Moreover, the striking results from the 42.85-h forced desynchrony protocol demonstrating the adverse effects of 28 consecutive hours of wakefulness on

neurobehavioral performance contributed to the design of a series of studies evaluating the impact of extended duration (>24 hour) work shifts on the risk of attentional failures, serious medical errors and accidents among interns working in U.S. hospitals. These studies were published in the New England Journal of Medicine this past year, as follows.

1. Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, Rothschild JM, Katz JT, Lilly CM, Stone PH, Aeschbach D, Czeisler CA; Harvard Work Hours, Health and Safety Group. Effect of reducing interns' weekly work hours on sleep and attentional failures. N Engl J Med. 2004;351:1829-1837.

2: Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, Lilly CM, Stone PH, Lockley SW, Bates DW, Czeisler CA. Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med. 2004;351:1838-1848.

3: Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, Czeisler CA; Harvard Work Hours, Health, and Safety Group. Extended work shifts and the risk of motor vehicle crashes among interns. N Engl J Med. 2005;352:125-134.

10. NEW DISCOVERIES, INVENTIONS, PATENTS

(1) Hypnion has filed multiple patents on key features of SCORE-2000™ and use of SCORE-2000™ (and like technologies) in preclinical drug discovery and evaluation, including secure, internet-based real-time systems biology approaches to accelerate biology-driven structure-activity relationships in pharmacology and medicinal chemistry. Patents have not been issued by the USPTO.

(2) Hypnion has invented and first brought to practice a novel telemetry-compliant fully automated sleep deprivation apparatus for preclinical drug discovery and evaluation that cost-effectively enables the study and differentiation of stimulant interaction with sleep loss. The system capitalizes on the wake-promoting potential of the righting reflex in the rat as a method to stimulate wakefulness. Hypnion has demonstrated that this apparatus, when coupled to an updated version of SCORE-2000™, applies sleep deprivation stimuli to effect, dramatically lowering the stress of sleep deprivation in laboratory rodents.

11. HONORS/AWARDS (n = 43)

CA Czeisler	Awarded Aschoff's Rule, 2001
CA Czeisler	E.H. Aherns, Jr. Lectureship Award, Association for Patient-Oriented Research, April 2002
CA Czeisler	William C. Dement Achievement Award from American Academy of Sleep Medicine, June 2002
CA Czeisler	Chair, Research Committee, Sleep Research Society, 2003
CA Czeisler	Spaulding Distinguished Lecture, Spaulding Hospital, Boston, MA, June 20 2003

CA Czeisler	President-Elect, Sleep Research Society, 2003
CA Czeisler	Appointed as Frank Baldino, Jr., Ph.D. Professor of Sleep Medicine, Harvard Medical School, 2004
CA Czeisler	President, Sleep Research Society, 2005
CA Czeisler	Spaulding Distinguished Lecture, Spaulding Hospital, Boston, MA, 2003
CA Czeisler	Member, Board of Directors, World Federation of Sleep Research and Sleep Medicine Societies, 2005
CA Czeisler	Member, Board of Directors, Associated Professional Sleep Societies, 2005
D Dean	Sleep Research Society Travel Award, 2002
DF Dinges	Professor of the Year, Biological Basis of Behavior Society, University of Pennsylvania, 2000
DF Dinges	NASA TIGR Aviation Safety Award to the Fatigue Countermeasures Project Team, 2000
DF Dinges	Team Leader, Neurobehavioral and Psychosocial Factors, National Space Biomedical Research Institute, 2000
DF Dinges	Senator Mark O. Hatfield Public Policy Award, American Academy of Sleep Medicine, 2001
DF Dinges	Keynote Address during the Plenary Session of the 16th Annual Meeting of the Associated Professional Sleep Societies, June 2002.
DF Dinges	William E. Collins Award, Aerospace Human Factors Association, 2003
DF Dinges	President, World Federation of Sleep Research Societies, 2003-2007
DF Dinges	Recipient of Decade of Behavior Research Award from the American Psychological Association, 2004
DF Dinges	Recipient of the American Academy of Sleep Medicine William C. Dement Academic Achievement Award, 2004
DF Dinges	Vukov Lecture, Oregon Health and Science University, Portland, OR, 2004
DF Dinges	Armstrong Lecture, Aerospace Medical Association, Anchorage, AK, 2004
DF Dinges	Elected Member, International Academy of Astronautics
DF Dinges	Member of Council, National Institute of Nursing Research, National Institutes of Health
DM Edgar	Hypnion issued $10MM in venture-backed Series-A funding based upon "exceptional innovation and promise as the first Sleep-Wake Biotechnology Company", September 2000.
DM Edgar	Hypnion issued $47MM in venture-backed Series-B funding based upon "exceptional research management, productivity, and innovation", March 2003.
DM Edgar	Promoted to "Chief Science & Technology Officer", Hypnion, Inc. March 2003.

DM Edgar	Hypnion named the #1 biotechnology investment in New England and rated the #3 biotechnology investment in the United States by the Boston Globe, March 2003.
DM Edgar	Hypnion named by Acumen Journal of Life Sciences as one of the 100 most influential biotechnology companies in the world, March, 2004.
SP Grady	Endocrine Fellows Foundation Grant, 6/2001
EB Klerman	Program committee, Society for Research in Biological Rhythms bi-annual meeting 2003-2004.
EB Klerman	Chair, Publications Committee, Sleep Research Society, 2004.
EB Klerman	Appointed Associate Director of the Brigham and Women's Hospital General Clinical Research Center in 2003.
EB Klerman	Named Director of the Biomathematical Modeling Unit within the Division of Sleep Medicine at the Brigham and Women's Hospital.
D Rodriguez	Sleep Research Society Travel Award, 2002
NL Rogers	Assistant Secretary, World Federation of Sleep Research Societies, 2003-2007
NL Rogers	Recipient of a National Health & Medical Research Council (NHMRC) of Australia Howard Florey Centenary Research Fellowship, 2004
NL Rogers	Recipient of a New South Wales BioFirst Award, 2004
H Van Dongen	Young Investigator Award, Sleep Research Society, 2003
H Van Dongen	Promoted to Research Associate Professor of Sleep and Chronobiology, University of Pennsylvania School of Medicine, 2004
JP Wisor	Promoted to the academic rank of Research Associate in the Department of Psychiatry, Stanford University, September 2000
KP Wright, Jr.	Young Investigator Award – American Academy of Sleep Medicine - Honorable mention, 6/2000.