Tiagabine is Associated With Sustained Attention During Sleep Restriction: Evidence for the Value of Slow-Wave Sleep Enhancement?

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Study Objectives: To evaluate the impact of enhanced slow-wave sleep (SWS) on behavioral, psychological, and physiologic changes resulting from sleep restriction

Design: A double-blind, parallel-group, placebo-controlled design was used to compare tiagabine, 8 mg, (a SWS-enhancing drug) to placebo during 4 nights of sleep restriction (time in bed = 5 hours per night). Behavioral, psychological, and physiologic measures of the impact of sleep restriction were compared between groups at baseline, during sleep restriction, and following recovery sleep.

Setting: Two sleep research laboratories.

Participants: Thirty-eight healthy adults; 9 men and 10 women (mean age: 26.0 ± 6.1 years) in the placebo group and 8 men and 11 women (mean age: 26.7 ± 8.1 years) in the tiagabine 8 mg group

Interventions: Both experimental groups underwent 4 nights of sleep restriction. Each group received either tiagabine 8 mg or placebo on all sleep-restriction nights, and both groups received placebo on baseline and recovery nights.

Measurements and Results: Polysomnography documented a SWS-enhancing effect of tiagabine. The placebo group displayed the predicted deficits due to sleep restriction on the Psychomotor Vigilance Task and the Multiple Sleep Latency Test. Compared with placebo, the tiagabine group did not demonstrate impairment in sustained attention on the Psychomotor Vigilance Task, performed better on the Wisconsin Card Sorting Task, reported more restorative sleep, and had less of an increase in afternoon-evening salivary free cortisol. Multiple Sleep Latency Test, ratings of sleepiness, recovery sleep, and other measures did not differ between groups.

Conclusions: To our knowledge these findings are the first to be consistent with the hypothesis that pharmacologic SWS enhancement reduces selective aspects of the behavioral, psychological, and physiologic impact of sleep restriction.

Keywords: Slow wave sleep, attention, sleepiness, performance, tiagabine

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INTRODUCTION

SYNCHRONIZED ELECTRICAL POTENTIALS IN THE ELECTROENCEPHALOGRAM (EEG), WHICH ARE CHARACTERISTIC OF NON-RAPID EYE MOVEMENT (NREM) sleep are felt to result from thalamocortical activity.1 Differential attention has been given to slow-wave sleep (SWS), slow-wave activity (SWA), or both, although the increased EEG synchrony in NREM extends beyond the SWA frequencies. This increased attention has largely resulted from the hypothesized role of SWS/SWA in sleep homeostatic regulation, prompted by a number of observations, including (1) enhanced SWS following sleep deprivation in proportion to the duration of prior wakefulness,2 (2) reduced amounts of SWA during nocturnal sleep following afternoon/evening naps,3 (3) a gradual decline in SWA across a night of sleep,4 and (4) increased SWS following nights of fragmented sleep.5 Within the 2-process model of sleep regulation, heightened SWS/SWA has been viewed as reflecting Process S, the homeostatic component.6 Many authors have proposed that increased SWS/SWA represents ongoing cortical recovery from prior wakefulness activities. That is, NREM sleep periods with more SWS/SWA have been widely hypothesized to be a time of relatively heightened neurophysiologic restoration or recuperation.7 Tononi and Cirelli8 hypothesized, more specifically, that SWS/SWA reflect synaptic changes necessary to conserve energy, save space for future synaptic growth, and enhance signal-to-noise ratio.

Selective deprivation of SWS (or stage 4 only) by a repetitive-arousal procedure has failed to support the enhanced recuperative “value” of SWS relative to other sleep stages. Neither
performance nor alertness has been found to be impaired after varying degrees (approximately 25%-90% vs baseline) of SWS reduction.10-12

In a prior study, which utilized the MSLT and performance tests to detect consequences of SWS deprivation and also controlled for the sleep fragmentation caused by the SWS deprivation procedure, no impact of SWS deprivation was found beyond that caused by sleep fragmentation.13 However, there was a suggestion from posthoc analyses of an interaction between SWS and sleep duration, such that sufficient SWS may protect against the adverse effects of mild to moderate sleep loss.

Drugs having a number of mechanisms of action have been found to increase SWS, SWA, or both SWS and SWA, including several antagonists of 5-HT_2 receptors; the α,δ calcium channel modulators gabapentin and pregabalin; gaboxadol, a selective (for α,δ receptors) extrasynaptic GABA<sub>A</sub> agonist; and tiagabine, a selective GABA reuptake inhibitor. Whether the increases in SWS/SWA with these drugs reflect the same, or more importantly similar, neural processes to those that characterize natural SWS/SWA is undetermined.

We chose to further explore the value of enhanced NREM EEG synchrony, as indexed by SWS, by administering tiagabine 8 mg during a period of sleep restriction. Tiagabine produces an increase in extracellular GABA by inhibiting reuptake on the GAT-1 transporter. Absorption of tiagabine is rapid, with a t<sub>max</sub> of about 45 minutes in the fasting state and an elimination half-life of 7 to 9 hours in patients not taking hepatic enzyme-inducing drugs. The primary metabolic pathway for tiagabine is CYP3A4, and the P450 system is neither induced nor inhibited. A dose of 8 mg was chosen to produce a significant increase in SWS with a low probability of next-day sedation. Residual sedative effects have not been noted with an 8-mg dose in middle-aged adults and a low probability of next-day sedation. Healthy elderly subjects have also been shown to be free of residual sedation with 8 mg, although elderly insomnia patients have been found to have mildly, but significantly, impaired psychomotor performance at this dose 1 hour after awakening. In none of the prior studies of tiagabine has daytime function been assessed beyond about 1 hour after morning rise time.

METHODS

Study Design and General Methods

A randomized, double-blind, placebo-controlled, parallel-groups design was used to compare tiagabine 8 mg and placebo. The study was conducted at 2 laboratories using an identical protocol. Each participant’s activities consisted of a screening visit, 8 consecutive nights and days of sleep-laboratory procedures: 1 screening/adaptation night, 1 baseline night (and screening/baseline day of testing), 4 sleep-restriction nights (and 2 testing days), 2 recovery nights (and 1 testing day), and end-of-study procedures. All subjects received single-blind placebo on screening and baseline nights as well as on all recovery nights. Subjects received placebo or tiagabine 8 mg (T8) in randomized double-blind fashion on the 4 sleep-restriction nights. Study drug was administered 30 minutes prior to scheduled bedtime. For each subject the study period was a minimum of 11 days and a maximum of 28 days from initial screening to follow-up. The protocol was approved by the institutional review board for each laboratory, and all subjects signed an informed consent and were compensated for participate-

tion. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Subject Recruitment and Screening

Media advertisements were used to recruit potential subjects. A general description of the study was provided and preliminary screening was conducted by telephone. Interested and qualified persons were scheduled for a clinical screening visit during which a thorough explanation of the study was provided and subjects gave written informed consent. Clinical screening procedures included a sleep, psychiatric, and medical history; physical examination; electrocardiogram; clinical laboratory testing (hematology, chemistry, urinalysis); and urine screen for drugs of abuse. These procedures ensured that subjects were free of chronic sleep disturbance; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition psychiatric diagnoses, including substance abuse in the past 2 years; and current or recent medical illness. Women could not be pregnant or lactating and had to confirm the use of adequate contraceptive procedures throughout the study.

During the prior 2 months the subjects must have maintained a bedtime between 9:00 PM and 1:00 AM at least 5 nights per week and a usual nightly sleep duration between 6.5 and 8.5 hours. An Epworth Sleepiness Scale score less than 15 and a body mass index between 19 and 32 kg/m<sup>2</sup>, inclusive, were also required.

Subjects could not work night or rotating shifts, or have crossed more than 3 time zones, in the prior 3 weeks. Subjects were also excluded if they used any psychotropic medication or sedating or alerting over-the-counter drugs during the prior week, usually consumed more than 3 alcohol-containing beverages (glasses of wine/beer or equivalent) or more than 300 mg of caffeine per day, or smoked more than 5 cigarettes a day and could not forego smoking for up to 14 hours while in the laboratory. Prior use of or allergy to tiagabine, participation in a clinical research trial within 30 days; history of a positive test for HIV, HBsAg, or anti-HCV; and blood donation within 30 days were additional exclusion criteria.

The screening visit included training on performance tests used in the study and completion of the Horne-Östberg Morningness-Eveningness Questionnaire and the Sleep Timing Questionnaire. Polysomnography (PSG) screening was performed during the first 2 nights in the sleep laboratory, and a Multiple Sleep Latency Test (MSLT) followed night 2. On night 1, respiratory recordings and leg electromyography were included. Participation was discontinued if, on PSG night 1, the apnea-hypopnea index was greater than 10 per hour or the periodic leg movement arousal index was greater than 10 per hour. On night 2, which also served as the baseline night, total sleep time (TST) was required to be 515 minutes or less (time in bed was 540 minutes), and the mean latency on the day 2 MSLT was required to be at least 8 minutes.

Sixty-nine individuals signed informed consent. Ten withdrew consent prior to randomization. Eighteen failed screening (13 MSLT, 4 medical, 1 positive drug screen). Forty-one healthy male and female subjects aged 18 to 40 inclusive, were randomly assigned to the 2 study groups. Three subjects were excluded following completion of the protocol, but prior to unblinding of study condition, because central scoring of the MSLT revealed that the subjects failed to meet the MSLT entry criterion. The data presented in this report were collected from 19 subjects taking
tiagabine and 19 subjects on placebo. As can be discerned from the characteristics contained in Table 1, at study entry, the groups did not differ in age, sex distribution, body mass index, habitual caffeine intake, morningness-eveningness (based on the Horne-Ostberg Questionnaire), and usual rise time and bedtime (based on the Sleep Timing Questionnaire).

**General Study Procedures**

Participation involved 8 consecutive nights and the intervening 7 days from laboratory screening to study completion for each subject. PSG nights 1 and 2 and the MSLT on day 2 (which followed night 2) were screening procedures. Night 2 PSG and day 2 MSLT also served as baseline measures, as did other measures from day 2. PSG recording time was 10 hours on night 1 (11:00 PM to 9:00 AM) and 9 hours on night 2 (11:00 PM to 8:00 AM). The durations of the recordings on nights 1 and 2 were selected to minimize the impact of any prior sleep debt on study results. Single-blind placebo was administered on both nights to all subjects, 30 minutes prior to bedtime. In the evening of night 2, subjects received additional training on the performance tests used in the study.

Subjects were randomly assigned to the 2 study groups after all screening and baseline procedures were completed. Group assignment was stratified to ensure approximate balance in age, sex, and BMI. Subjects who did not differ in age, sex distribution, body mass index, habitual caffeine intake, morningness-eveningness (based on the Horne-Ostberg Questionnaire), and usual rise time and bedtime were included in the study.

| Table 1 – Demographic and Baseline Characteristics of the Study Groups |
|------------------------|------------------------|------------------------|
|                        | Placebo (N = 19) | Tiagabine (N = 19) |
| Mean (SD) Age in years | 26.0 (6.1) | 26.7 (8.1) |
| Male / Female           | 9 / 10     | 8 / 11      |
| Mean (SD) BMI, kg/m²    | 24.7 (3.0) | 25.6 (3.5) |
| Morningness-Eveningness, no. pts^a | Moderate Morning 6 3 | Moderate Evening 2 2 |
| Sleep Timing:^b         | Mean Bedtime 11:24 PM | 11:32 PM |
|                        | Mean Rise time 7:52 AM | 8:06 AM |
| Mean (SD) ESS Score^c | 4.5 (2.4) | 5.8 (3.0) |
| Mean (SD) Day 2 MSLT, min. | 13.4 (4.0) | 13.8 (4.6) |
| Mean (SD) Night 2 TST, min. | 479.8 (25.9) | 479.8 (31.6) |

^aFrom the Horne and Ostberg Questionnaire at baseline
^bFrom the Sleep Timing Questionnaire at baseline
^cEpworth Sleepiness Scale at baseline

diagnostic samples (days 5 and 6).

All subjects received single-blind placebo on nights 7 and 8 at 9:30 PM. PSGs were recorded from 10:00 PM to 10:00 AM. Twelve hours were allotted to observe the potential differential effects of sleep restriction with and without tiagabine upon extent of recovery sleep (a known measure of homeostatic sleep drive). On day 7 (between nights 7 and 8) MSLT subjective scales and performance, mood, and executive function tests were completed. Urine and saliva samples and electrocardiographic data were collected.

Alcohol was prohibited beginning 48 hours prior to laboratory night 1 for the duration of participation. Caffeine consumption on study days 1, 3, and 4 was limited to a single drink within 1 hour of morning awakening. No caffeine was allowed on the remaining study days. Vigorous exercise was prohibited on study days 2, 5, 6, and 7.

**Polysomnography**

Digital recordings were made on all 8 study nights. The recording montage for all nights included the following: right and left electrooculogram, submental electromyogram, electrocardiogram (V5), and 10 EEG derivations (C3-A2, C4-A1, O1-A2, O2-A1, FP1-A2, FP2-A1, F3-A2, F4-A1, F7-A2, F8-A1). On night 1, the recording also included nasal thermocouple, oximetry, respiratory movement, and right and left anterior tibialis electromyogram. Sampling rate for all EEG signals was 200 HZ. All PSGs were scored at 1 study site according to standard methods using the C3/A2 derivation. Each subject’s PSGs were scored by a single scorer. Spectral analysis of the multiple EEG derivations will be performed for future reports.

**Daytime Testing**

The MSLT evaluates sleep propensity by electrophysiologically measuring the latency to fall asleep at multiple times throughout the day. MSLT subtests were conducted at 10:00 AM, 12:00 PM, 2:00 PM, 4:00 PM and 6:00 PM on days 2, 5, 6, and 7. MSLTs were conducted following standard procedures, and all MSLTs for the study were scored by a single scorer. The Psychomotor Vigilance Task (PVT) is a 10-minute, simple reaction time test that measures sustained attention and psychomotor function. The PVT was given at 10:40 AM, 12:30 PM, 2:40 PM, and 4:40 PM on days 2, 5, 6, and 7. Dependent variables include lapses (reaction time > 500 milliseconds), mean of the slowest 10% reaction times, mean of the fastest 10% reaction times, and mean reaction time.

The Profile of Mood States (POMS) is a self-administered questionnaire that measures 6 dimensions of affect or mood. Subjects rate how they feel “now” with respect to 65 adjectives on a 5-point scale (0 = “not at all”, 4 = “extremely”). The POMS was completed at 11:50 AM and 1:50 PM on days 2, 5, 6, and 7. The Karolinska Sleepiness Scale (KSS) is a 9-point rating scale that provides a subjective measurement of sleepiness. The KSS was completed approximately 2 minutes prior to each MSLT subtest.

The Buschke Selective Reminding Test (BSRT) assesses verbal learning and memory via 6 immediate and 1 delayed recall trials to assess retention. Each trial requires the subject to repeat and recall a list of 12 words, is subject paced, and usually takes 1 to
2 minutes. The BSRT was administered at 2:30 PM, with delayed recall at 3:00 PM on days 2, 5, 6, and 7. The dependent measures are the number of correct responses on the sixth immediate recall trial and on the delayed recall trial.

The N-Back Task\textsuperscript{39} is a visual working-memory task that requires the subject to compare the spatial position of a 200-millisecond stimulus with the position of the previous stimulus (1-Back) or to the position 2 stimuli previously (2-Back). Stimulus presentation is computer paced, with a constant 4.5-second interstimulus interval. Administration times were 11:00 AM and 5:00 PM on days 2, 5, 6, and 7. Each administration included a 1-Back trial and a 2-Back trial, each with a duration of approximately 4 minutes. The variables of interest include the number of correct and incorrect matches and nonmatches, total correct and incorrect responses, and the mean reaction times for both correct and incorrect matches and nonmatches.

The Paced Auditory Serial Addition Test (PASAT)\textsuperscript{36,37} involves auditory perception and processing, speech production, working memory, and attention. Each administration consisted of 4 trials of 60 single-digit numbers presented by prerecorded audiobrade; the subject is instructed to add the 2 most recently heard numbers and give a verbal response. The 4 trials are experimenter paced, with decreasing interstimulus intervals of 2.4, 2, 1.6, and 1.2 seconds. Trials last approximately 1.2 to 2.4 minutes and are separated by 1-minute breaks. Dependent variables are the number of correct responses at each test speed and at all speeds combined. The PASAT was given at 9:00 AM and 3:10 PM on days 2, 5, and 6 and only at 3:10 PM on day 7.

The Raven’s Progressive Matrices is a measure of nonverbal fluid reasoning and general intellectual ability.\textsuperscript{38} It involves presentation of a series of gridded patterns that the subject completes by selecting the correct response from 5 possible choices. The test is subject paced, and typical administration time is 20 to 30 minutes. Because only 2 versions exist, Raven’s was presented only on days 2 and 6 at 7:30 PM. Order was counterbalanced equally between groups.

The Torrance Tests of Creative Thinking (TTCT) – Verbal Scale evaluates creativity by determining the interrelationship among verbal fluency, originality, and flexibility.\textsuperscript{39} Two comparable versions exist and were presented in counterbalanced fashion (equally between groups) on days 2 and 6 at 8:10 PM. Each administration consists of 6 subject-paced sections, 4 of which take about 5 minutes and 2 of which take about 10 minutes. With breaks between sections, total administration time is approximately 45 to 50 minutes. Dependent measures are standard scores for fluency, flexibility, and originality.

The Wisconsin Card Sorting Test (WCST) assesses concept formation and abstraction ability by having the subject identify 3 predetermined criterion principles.\textsuperscript{40} The task is subject paced, but stimuli are presented continuously until the principles have been identified. Typical task duration is 20-30 minutes. Duplicate forms are not available for this test and it was administered once to each subject at 8:00 AM on day 6. Variables of interest include total number of trials, trials to completion of the first level, total errors, and perseverative errors.

Heart rate variability recordings were made for 8 minutes starting approximately 20 minutes before each MSLT subtest. A single electrocardiogram tracing was recorded and stored digitally with a sampling rate of 200 Hz. Subjects were instructed to lie still with their eyes open and to remain awake. This report does not include heart rate variability data.

Salivary cortisol samples were collected hourly from 2:20 PM to 9:20 PM on days 2, 6, and 7. No food or drink was allowed for 30 minutes before each sample collection. Subjects inserted a salivette (Sarstedt AG & Co., Numbrecht, Germany) into their mouth. The salivette was chewed until the subject could no longer prevent swallowing excess saliva. The salivette was then placed in a tube, weighed to assure adequate saturation, and then stored at -20°C until shipped to Esoterix for analysis by radioimmunoassay.

Urine catecholamine determinations were made from 2 contiguous 12-hour aliquots (10:00 PM to 10:00 AM and 10:00 AM to 10:00 PM) on night 2/day 2, night 6/day 6, and night 7/day 7. Subjects collected all urine for each aliquot in a single container that contained 6N hydrochloric acid (Fisher Scientific, Pittsburgh, PA) to preserve the specimen. At the end of each aliquot, approximately 50 mL of the well-mixed specimen was poured into a sealed container and stored at -20°C until sent to Esoterix for analysis by high performance liquid chromatography.

**Statistical Analyses**

Baseline demographic, Epworth Sleepiness Scale, Morning-Eveningness Questionnaire, Sleep Timing Questionnaire, and PSG variables were compared between groups with analysis of variance (ANOVA) for continuous measures and $\chi^2$ for categoric variables. For data with multiple nights/days or administration times, mixed-model ANOVAs were used with factors for group, night or day, and time of day. The effects of sleep restriction and study drug on PSG variables were evaluated in a group (placebo, T8) × night (night 2, mean of nights 3-6) ANOVA. Similarly, group × day (day 2, day 5, day 6) × time of day ANOVAs were used for MSLT, PVT, and other daytime measures. For PSG variables, recovery from sleep restriction was examined with ANOVA with terms for group (T8, placebo) and night (night 2, night 7, night 8). For daytime assessments during recovery, ANOVAs, with terms for group, day (day 2, day 7), and time of day were used. For variables with large interindividual variability (stage 3, stage 4, SWS, PVT, MSLT, most neurocognitive measures) group differences were examined a priori by ANOVAs on change from baseline values. For these variables, significant group differences were followed up by examination of within-subjects factors for each group individually using polynomial contrasts. For within-subjects factors, the Huynh-Feldt adjustment was used to control for sphericity and Dunn-Sidak correction was used for multiple comparisons. For PSG variables other than stage 3, stage 4, and SWS, group differences during sleep restriction (nights 3-6) were evaluated by univariate ANOVAs on raw scores, rather than change scores, because of the significant influence of variable time in bed across nights. Univariate ANOVA was used for analysis of WCST variables because of the lack of baseline data. Pearson product moment correlations were calculated to explore the association of SWS to many of the daytime behavioral and physiologic variables.

**RESULTS**

**Polysomnography**

Mean PSG data for baseline, sleep restriction, and recovery
nights for both groups are shown in Table 2. Baseline PSG measures did not differ between groups. Significant main effects of night (night 2 versus mean of nights 3-6) indicate that sleep restriction resulted in the predicted decreases in TST, stage 1, stage 2, rapid eye movement (REM), wake after sleep onset (WASO), number of stage shifts to wake or stage 1, and latency to persistent sleep (p < .001 for all). Significant night × group interactions were found for stage 3 (F_{1,36} = 16.7, p < .001), stage 4 (F_{1,36} = 12.6, p = .001), and SWS (stage 3 plus stage 4; F_{1,36} = 21.4, p < .001) and are accounted for by differences during sleep restriction (mean of nights 3-6). Stage 3, stage 4, and SWS (change from baseline) were greater during sleep restriction for T8 (p < .001 for all) than for placebo. Compared with baseline, T8 averaged 29.1 (+23.8) more minutes of SWS on nights 3 to 6, whereas the placebo group averaged 5.4 (+22.1) fewer minutes (see Figure 1). This represents a mean increase in SWS from baseline of 40.9% with T8, as compared with a mean reduction from baseline of -6.4% with placebo, despite approximately 200 minutes more TST at baseline. There were no differences between groups during sleep restriction (nights 3-6) for TST, WASO, latency to persistent sleep, minutes or percentage of stage 1 or 2, or number of stage shifts to wake or stage 1.

Examination of recovery nights revealed significant differences

**Table 2—Polysomnography Variables for Placebo (PBO) and Tiagabine 8 mg (T8) Groups on Nights 2-8**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Sleep Restriction</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Night 2</td>
<td>Night 3</td>
<td>Night 4</td>
</tr>
<tr>
<td>PBO T8</td>
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<td></td>
<td></td>
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<tr>
<td>TST</td>
<td>479.8</td>
<td>274.0</td>
<td>286.2</td>
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<tr>
<td>(25.9)</td>
<td>(16.9)</td>
<td>(7.4)</td>
<td>(7.0)</td>
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<tr>
<td>Stage Min</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wake</td>
<td>60.2</td>
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<td>13.8</td>
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<tr>
<td>(25.9)</td>
<td>(16.9)</td>
<td>(7.4)</td>
<td>(7.0)</td>
</tr>
<tr>
<td>Stage 1</td>
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<td>(36.7)</td>
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<td>(12.4)</td>
<td>(9.7)</td>
<td>(9.5)</td>
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<td>REM</td>
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<td>(19.0)</td>
<td>(12.2)</td>
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<td>WASO</td>
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<tr>
<td>(25.8)</td>
<td>(15.0)</td>
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<td>LPS</td>
<td>19.8</td>
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<td>(14.3)</td>
<td>(16.2)</td>
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<td>Stage Shifts to, no.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wake</td>
<td>34.3</td>
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<td>(8.8)</td>
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<td>(7.7)</td>
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<td>40.1</td>
<td>19.1</td>
<td>19.7</td>
</tr>
<tr>
<td>(11.7)</td>
<td>(6.1)</td>
<td>(8.4)</td>
<td>(9.1)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD); TST, total sleep time; REM, rapid eye movement; WASO, wake after sleep onset; LPS, latency to persistent sleep.

1. Night 2 > mean of nights 3-6, p < .001
2. T8 > PBO, change from baseline night 2 to sleep restriction nights 3-6, p < .001
3. Night 2 < night 7 and night 8, p < .01
4. Night 2 < night 7, p < .02
5. Night 2 < night 8, p < .01
6. Night 7 < night 8, p < .008
7. Night 7 > night 8, p < .001

Figure 1—Change from baseline to nights 3 to 8 in minutes of slow-wave sleep (SWS) for both study groups. Time in bed varied across nights (9 hours on baseline night 2, 5 hours on nights 3 to 6, 12 hours on nights 7 and 8). Change from baseline in SWS was significantly greater for the tiagabine 8-mg group, as compared with the placebo group, on nights 3 to 6 (p < .001) and did not differ on nights 7 and 8.
The absence of a significant group × night interaction indicates that neither the amount nor structure of recovery sleep differed between groups. Compared to baseline, on recovery nights there were increases in TST, wake, stage 2, REM, and WASO on both night 7 (p < .001 to .025) and night 8 (p < .001 for all), reflecting both the recovery process and the increased time in bed on recovery nights. However, stage 3, stage 4, and SWS increased only on night 7 (p = .064, .012, .001, respectively) and were no different than baseline by night 8. This finding suggests that the recovery process was stronger on night 7 than on night 8 and is consistent with decreases from night 7 to night 8 in TST (p < .001), stage 2, (p < .001), stage 3 (p = .008), stage 4 (p = .001), and REM (p < .001) sleep, whereas WASO and latency to persistent sleep increased (p < .001 for both nights).

Correlation analyses did not reveal an association between any daytime variable and either the absolute minutes of SWS (on either night 6 or the mean of nights 3-6), or the change from baseline in minutes of SWS (change to either night 6 or to the mean of nights 3-6).

**Multiple Sleep Latency Test**

Sleep restriction resulted in marked decreases in MSLT latencies (F\textsubscript{2,68} = 117.2; p < .001) but no main group effect or group interactions (day × group F\textsubscript{2,68} = 0.17, p = .84). There was a main effect of time (F\textsubscript{4,136} = 6.63, p < .001) and a time x day interaction (F\textsubscript{8,272} = 3.38, p = .003). Mean ± SD MSLT latencies at baseline for the placebo and T8 groups were 13.4 ± 4.0 minutes and 13.8 ± 4.6 minutes, respectively. During sleep restriction, mean MSLT latencies on days 5 and 6 fell to 5.2 ± 3.4 and 4.3 ± 3.6 minutes for the T8 group and 5.4 ± 3.3 and 5.0 ± 3.4 minutes for the placebo group.

Comparison of baseline and recovery excluded the 10:00 AM MSLT subtest on day 2, since there was no comparable subtest on day 7 (night 7 PSG ended at 10:00 AM). ANOVA showed main effects for day (F\textsubscript{1,34} = 6.6, p = .015) and time (F\textsubscript{3,102} = 6.48; p < .001), and a day x time x group interaction (F\textsubscript{3,102} = 3.01, p = .034). Mean MSLT latencies were lower at baseline (placebo = 12.7 ± 4.2 min; T8 = 13.7 ± 4.7 min) than at recovery (placebo

**Figure 2**—Psychomotor vigilance task (PVT) data at baseline (day 2), during sleep restriction (days 5 and 6), and after recovery sleep (day 7). Panel A: mean (± SEM) reaction time. Change from baseline in reaction time was greater (i.e., slower reaction time) for the placebo group than for the tiagabine group on day 6, p = .024. Panel B: mean (± SEM) reaction time for the slowest 10% of responses. Placebo > tiagabine 8mg (change from baseline) on day 6, p = .025. Panel C: transformed number of lapses. Placebo > tiagabine 8mg (change from baseline) on day 6, p = .012; on day 5, p = .056.

**Figure 3**—Mean (± SEM) change from baseline to all other study nights in the subjective rating of restorative nature of sleep. A negative change score reflects lower restorative ratings. The placebo group rated the nature of sleep as significantly less restorative on nights 3 to 6 than did the tiagabine 8-mg group (p < .001).
Table 3 – Mean (SD) scores for the Wisconsin Card Sorting Task for the tiagabine and placebo groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Trials</th>
<th>Total Errors</th>
<th>Perservative Errors</th>
<th>Trials to Complete First Category</th>
<th>Percent Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiagabine</td>
<td>82.2</td>
<td>13.7</td>
<td>6.8</td>
<td>11.5</td>
<td>84.2</td>
</tr>
<tr>
<td>(N=17)</td>
<td>(15.1)</td>
<td>(8.9)</td>
<td>(3.8)</td>
<td>(1.0)</td>
<td>(6.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>95.7</td>
<td>21.7</td>
<td>10.9</td>
<td>14.8</td>
<td>79.0</td>
</tr>
<tr>
<td>(N=18)</td>
<td>(20.9)</td>
<td>(13.3)</td>
<td>(7.1)</td>
<td>(4.5)</td>
<td>(8.9)</td>
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<tr>
<td>p value</td>
<td>.036</td>
<td>.047</td>
<td>.044</td>
<td>.007</td>
<td>.049</td>
</tr>
</tbody>
</table>

= 14.0 ± 4.0 min; T8 = 16.3 ± 3.2 min. Placebo latencies were shorter than T8 at 4:00 PM (p = .024) and 6:00 PM (p = .027) on day 7.

Psychomotor Vigilance Task

Figure 2 displays PVT data. Square-root transformation was applied to lapse data, and reciprocal transformation was applied to slowest 10% reaction-time data. Analysis of sleep-restriction effects on square-root-transformed lapses revealed a main effect for day (F1,32 = 10.5, p < .001) and a day x group interaction (F1,32 = 4.8, p = .014). Examination of change (from baseline) scores showed a significant difference between groups on day 6 (p = .012) and a trend for a significant difference on day 5 (p = .056). The placebo group showed a progressive increase in lapse frequency (linear contrast p = .003) from day 2 to day 5 to day 6, whereas the performance of the T8 group remained essentially constant.

Both slowest 10% reaction time and mean reaction time showed a significant effect of day (F1,32 = 15.7 and F2,68 = 14.2, p < .001 for each) and day x group interactions (F2,68 = 3.5, p = .046; F2,68 = 3.4, p = .039, respectively). There were no significant time, x group, or day x time x group effects. Examination of change (from baseline) scores showed significant group effects for slowest 10% reaction time and mean reaction time on day 6 (p = .024 and .025, respectively) but not on day 5. The placebo group showed progressive increases in slowest 10% and mean reaction times (p < .002 for both), whereas the T8 group failed to show a significant change from baseline. That is, the expected deterioration in PVT performance with sleep restriction was observed in the placebo group but was not seen or was markedly attenuated in the T8 group. From baseline to day 6, the mean reaction time increased 17% for the placebo group and 4% for the T8 group, the mean number of transformed lapses increased 91% for the placebo group and 13% for the T8 group, and the mean of the slowest 10% of responses increased 44% for the placebo group and 6% for the T8 group.

Comparison of baseline and recovery data revealed a day x group interaction (F1,32 = 3.1, p = .023) for transformed lapses. Expressed as change from baseline, the placebo group made more lapses than the T8 group. Slowest 10% and mean reaction time data were similar for both groups on day 7 compared with day 2.

Two subjects (1 in each group) had a very high number of total errors on the PVT, indicating poor compliance with study instructions; however their other PVT data were not atypical. All of the statistical analyses were repeated after exclusion of data from these subjects without change in the significant findings.

Self-Reported Ratings of Sleep and Waking

Analysis of the rating of the restorative nature of sleep (obtained from the morning questionnaire) produced a night x group interaction (F1,36 = 9.9, p = .005) as well as a night effect (F1,26 = 26.6, p < .001). The decline from baseline to sleep restriction was greater for the placebo group (mean change score = −1.36 ± 1.0) than for the T8 group (mean change score = −0.36 ± 1.0; see Figure 3). Sleep restriction produced decreased morning ratings of ability to concentrate and level of alertness (F1,36 = 41.3, 17.1, respectively, p < .001 for both) but no differences between groups.

Two of 6 POMS scales changed significantly with sleep restriction. Fatigue/inertia (F2,70 = 19.2, p < .001) increased, and vigor/activity (F2,70 = 5.24, p = .016) decreased. There was a nonsignificant trend for anger/hostility to increase (p = .082). Except for depression/dejection, which showed a group effect (F1,35 = 4.2, p = .047), there were no significant group or day x group interactions, although the placebo group tended to score higher than the T8 group on day 6 on tension/anxiety (p = .06) and fatigue/inertia (p = .09). Since the placebo group tended to score higher than the T8 group on depression/dejection at baseline (p = .089), we looked at change from baseline to evaluate the effect of drug during sleep restriction. No group difference was noted. Fatigue/inertia decreased below baseline levels on recovery day 7 (F1,34 = 4.2, p = .028) but no group, day, or day x group effects were noted for the remaining POMS scales during recovery.

KSS ratings of sleepiness increased significantly from day 2 to days 5 and 6 (F2,68 = 81.1, p < .001) and decreased from morning to evening (F1,34 = 11.4, p < .001). There were no significant group differences or interactions. KSS ratings on recovery day 7 did not differ from day 2 for either group.

Executive Function Measures

WCST data (collected at 8:00 AM on day 6) for 2 subjects (1 in each group) were lost because of technical error. Another subject’s data were excluded prior to unblinding because his scores on 4 of 5 analyzed variables were 3.6 to 5.3 standard deviations from the mean of the remaining 35 subjects. Mean data for the remaining 35 subjects are contained in Table 3, along with the statistical results. T8 subjects took significantly fewer trials to complete the first category (p = .007) and all categories (p = .036) and committed fewer total errors (p = .047) and perseverative errors (p = .044). The T8 group also had a higher correct response rate than did the placebo group (p = .049).

ANOVA showed significant main effects of sleep restriction for 2 of the individual scales of the TTCT-Verbal, as well as the average of the 3 scales. Flexibility (F1,34 = 9.8, p = .008), fluency (F1,34 = 8.1, p = .004), and average (F1,34 = 7.4, p = .01) declined significantly from day 2 to day 6 with sleep restriction. Originality showed a trend in the same direction (F1,34 = 3.7, p = .062). However, there were no group differences or interactions.

Other Cognitive Tests

Sleep restriction and study drug had no effect on BSR test learning or recall. Comparison of baseline and recovery showed a significant effect of day (F1,32 = 4.7, p = .037) and a trend for a day x group interaction (F1,32 = 3.1, p = .087). Groups did not differ on day 2, but the placebo group (7.8 ± 3.0) tended to recall fewer
words than the T8 group (9.1 ± 3.6) on day 7 (p = .074). PASAT, Raven’s Matrices, and the N-Back task did not show a reliable effect of sleep restriction, and, once baseline differences were accounted for, no group differences were identified for any variable on these tests. In fact, there was evidence of improved performance, suggesting a learning effect for all 3 measures.

Salivary Cortisol and Urinary Catecholamines

Salivary free-cortisol data from 2 subjects were excluded because of multiple missing values, or because their data were markedly outside physiologic ranges, suggesting loss of sample integrity. Data for day 7 of a third subject were excluded because 2 values were outside the physiologic range. When considering the entire sampling period from 2:20 PM to 9:20 PM, overall cortisol levels showed a day x group interaction (F_{1,28} = 4.8, p = .037) and a main effect of time (F_{1,196} = 2.4, p = .036). The change from baseline in overall cortisol levels was increased for the placebo group compared with the T8 group (p = .037). Mean change from baseline levels were .031 ± .05 µg/dL for the placebo group and -.005 ± .03 µg/dL for the T8 group. Comparison of mean change from baseline in area under the curve revealed a significant group effect (F_{1,12} = 4.4, p < .044), with the placebo group showing a greater increase in area under the curve than the T8 group. Day 7 cortisol change-score data showed no main effect of group or day, nor an interaction.

Urinary catecholamine values, expressed as a ratio of creatinine, did not differ between groups, or as a function of day or time of day. No interactions were found. This was true whether 12-hour aliquots were analyzed separately or means for 24-hour periods were determined and analyzed.

DISCUSSION

Tiagabine consistently increased SWS during the 4-night sleep restriction period, relative to both baseline and placebo values. Whether this represents only an electroencephalographic change, or an enhancement of the essential physiologic processes associated with NREM sleep is the essence of our inquiry. Several results are consistent with the hypothesis that enhancement of SWS via administration of T8 increases or intensifies at least some functional component or components of NREM sleep. First, no other differences in sleep were identified during the sleep-restriction period, including amount of stage 1 sleep and the number of sleep-stage shifts to wake or to stage 1 sleep. The absence of a group difference on the latter 2 variables indicates that tiagabine effects were not mediated through a reduction in sleep fragmentation. Second, T8 use during a period of sleep restriction preserved sustained attention performance on the PVT at baseline levels, whereas, with placebo, PVT performance declined markedly, as expected. Even after 1 night of recovery sleep, PVT lapses remained elevated compared with baseline for the placebo group but not for the T8 group. Third, the T8 group scored significantly higher than the placebo group on key WCST measures, which require sustained executive function. Fourth, subject ratings of the restorative nature of sleep on sleep-restriction nights with T8 were significantly higher than with placebo, and the fatigue/inertia scale of the POMS showed a trend toward less fatigue in the T8 group than in the placebo group during sleep restriction. Finally, salivary free-cortisol was elevated relative to baseline in the placebo group but not in the T8 group.

Alternative hypotheses for the observed results include a direct effect of T8 and the possibility of type I error. Accounting for the PVT, WCST, and restorative rating observations by a direct drug effect would seem extremely implausible. Given the 7- to 9-hour half-life of tiagabine and the well-documented GABAergic mechanism of action, which in some studies produces increased TST and reduced WASO, the expected direct effect of the drug on PVT and WCST performance would be impairment. Morning ratings of “restoration from sleep” were made only 6 hours after drug ingestion, at a time when a direct drug effect would be sedating and, presumably, subjects would feel less restored.

The possibility of type I error relates to the use of multiple measures of daytime performance, 4 of which showed no differences between groups. Several points allow us to reject, with reasonable confidence, type I error as the explanation of our findings. First, all significant group differences were in the same direction, i.e., T8 superior to placebo. Second, 3 PVT measures documented to be sensitive to instability of attention commonly seen with sleep loss differentiated the 2 groups. Third, most other performance measures were not sensitive to sleep restriction in this study. The absence of a deficit on these measures with sleep restriction prevents possible differences between groups. Fourth, key psychometric properties of the PVT and WCST make them more sensitive to variation in sustained attention than do the other measures used, in particular, task duration, experimenter pacing, and cognitive domain assessed. Perhaps, most importantly, there was thematic orderliness in the results. Physiologic and retrospective assays of sleepiness, specifically the MSLT, recovery sleep, and KSS, were unaffected by the increase in SWS with T8. In contrast, the measures of sustained attention did discriminate between groups.

The commonalities of the PVT and WCST are longer task duration and the need for sustained attention. The PVT is well documented as being sensitive to instability in attention, is 10 minutes in duration, and is experimenter paced with variable interstimulus intervals. The WCST assesses concept formation and abstraction ability and uniquely involves sustained executive function for 20 or more minutes, on the average. All of the other performance assessments used in this investigation were subject paced, lasted only 1 to 4 minutes, and/or had fixed interstimulus intervals, factors that reduce or eliminate the effect of sleep loss on performance because sustained attention is much less critical. Indeed, the degree of sleep restriction produced by the experimental manipulation did not produce impairment on these measures of waking function.

Because only 1 version of the WCST exists, no baseline assessment was possible. Although it is conceivable that the group differences observed were related to basal differences between groups rather than a differential response to sleep restriction, this seems unlikely given the uniformity between groups on other baseline evaluations. In particular, the groups were equivalent on all 3 scales and the average score of the TTCT-V and also on Raven’s Matrices (both speed and accuracy), which are influenced by general intellectual ability. Baseline performance on the PASAT, N-Back, and BSRT, which are measures of learning, working memory, and delayed recall, was also comparable between groups. Because the 2 groups appeared similar at baseline in cognitive ability and because the WCST uniquely involves sustained executive attention, the observed group differences are best explained by the effects of experimental manipulations.
Salivary free-cortisol levels on day 6 were increased after sleep restriction relative to baseline in the placebo group, but, in the T8 group the levels were stable. Studies of the impact of sleep restriction on next-day cortisol levels have not produced consistent results. Leproult et al\textsuperscript{41} found elevated plasma cortisol levels from 6:00 PM to 11:00 PM on the evening following a single night of sleep restriction to 4 hours. Elevated evening (4:00 PM-9:00 PM) salivary cortisol levels have also been reported after 6 consecutive nights of sleep restriction to 4 hours per night.\textsuperscript{42} In contrast, reduced morning (4:30 AM to 9:30 AM) plasma cortisol values have been reported by Vgontzas et al\textsuperscript{43} after a 1-week limitation of sleep to 6 hours per night. The reason for the discrepancy in the literature is not immediately apparent; however, our data appear to be reasonably consistent with those of Leproult et al\textsuperscript{41} and Spiegel et al\textsuperscript{42} It has been hypothesized that increased daytime cortisol after sleep restriction results from decreased negative feedback regulation of the hypothalamus-pituitary-adrenal axis.\textsuperscript{44} The inhibitory modulation of cortisol secretion by sleep, and particularly SWS, is well documented.\textsuperscript{45} Enhancement of SWS in this study may have counteracted the loss of hypothalamic-pituitary-adrenal regulation seen with sleep restriction.

Failure to demonstrate a correlation between absolute amount of SWS or change from baseline in SWS and any of the measures of daytime function could be viewed as evidence that the demonstrated effects of tiagabine are not mediated by SWS. However, EEG representation of a physiologic process may or may not correlate with other components of that process. One example is the observation that, although benzodiazepines reduce SWS, growth hormone secretion (which may be a component of the SWS process) is unaffected.\textsuperscript{46} Statistical correlation lends support to an interpretation of association between 2 variables but does not define an association. A priori experimental manipulation of an independent variable with sensitive measurement of a dependent variable, as performed in the present investigation, is generally felt to be a more rigorous scientific approach for demonstrating associations.

If T8 did enhance restorative aspects of NREM sleep, why did sleep propensity on the MSLT and subjective sleepiness on the KSS not differ from placebo? Several possible explanations exist, including a lack of sensitivity of these measures to detect differences in sleepiness when homeostatic drive is very high as in the present study. Alternatively, the differential influence of increased SWS on measures of sustained attention versus measures of sleep propensity may relate directly to the function of SWS (i.e., enhanced EEG synchrony during sleep).

Any discussion of SWS function must consider the predictable reduction in SWS amount with normal aging, because a parallel decline in the restorative value of sleep has not been documented. Investigators have described that the SWS decline is predominantly, if not exclusively, the result of changes in EEG amplitude, with EEG frequency patterns remaining constant with healthy aging. As discussed recently by Bliwise,\textsuperscript{47} the loss in EEG amplitude may reflect age-related changes in neuroendocrine or other humorally mediated factors rather than a change in the restorative capacity of sleep. On the other hand, the EEG frequency pattern (which does not change with age) closely associated with neuronal synchrony may relate to certain aspects of restoration. Similarly drug-related reductions in SWS, such as those seen with benzodiazepines, are predominantly the result of EEG wave-amplitude reduction rather than EEG frequency alterations.\textsuperscript{48}

It is also important to consider prior studies which have failed to demonstrate an effect of SWS deprivation (more accurately SWS reduction) on daytime function. Inspection of these studies reveals significant methodological limitations which may account for the negative findings of these studies. For example, one study\textsuperscript{49} attempted to compare the impact on daytime performance of sleep disruption with and without SWS in 12 subjects; however, the experimental technique produced more than a 50% reduction in SWS in the “control” condition (i.e., designed to retain SWS), versus a 85% reduction in the “no-SWS” condition. Finding differences in performance between two conditions with 50% and 85% reductions of SWS, with the additional influence of approximately 55-65 experimental arousals per night and total sleep times on disruption nights which range from 368 to 400 minutes in both conditions, would be unlikely and at least require a very large sample size.

Studies by Lubin et al\textsuperscript{50} and Johnson et al\textsuperscript{51} deprived subjects of stage 4, not SWS, and, therefore, considerable SWS occurred. Compared with baseline, SWS was reduced by 78% and 63% in the 2 studies, respectively. Moreover, the sample size per experimental condition in the Lubin et al study was 4 and, in the Johnson et al study, was 7. The statistical power to detect differences in performance associated with sleep-stage differences when sleep is highly disrupted by the experimental procedures is likely to be exceedingly low. Similar concerns exist for the other SWS-deprivation studies.\textsuperscript{10}

EEG synchrony during NREM sleep has been hypothesized to be critical for reversing cortical synaptic potentiation that occurs during wakefulness.\textsuperscript{9,52} Reversal of cortical synaptic potentiation may be a process through which sleep facilitates memory, learning, sustained attention, and other cortical functions.\textsuperscript{51,52} There is evidence that sleep, and specifically SWS, is particularly important for the prefrontal cortex,\textsuperscript{53} which is primarily involved in higher cognitive processes, and that SWS is differentially enhanced in anterior cortical areas following sleep deprivation.\textsuperscript{54,55}

Although increased wakefulness, and more specifically the level of central nervous system stimulation during wakefulness, is associated with synaptic potentiation, sleep loss per se probably does not increase cortical synaptic density. Therefore, variation in sleep propensity or homeostatic sleep drive, known to be closely related to magnitude of sleep loss and accurately measured by the MSLT, may be substantially independent from cortical synaptic potentiation and the reversal hypothesized to occur during SWS. From this viewpoint, the increase in SWS following sleep deprivation would more accurately be explained as a response to increased central nervous system stimulation during prior wakefulness, as opposed to an increase in homeostatic sleep drive. By increasing SWS, T8 may preserve sustained attention capability despite increased homeostatic sleep drive. In contrast, increased homeostatic sleep drive is likely to be directly dependent upon prior sleep history and mediated by other processes, including the accumulation of adenosine in the basal forebrain and near the ventrolateral preoptic nucleus.\textsuperscript{56,57}

A functional brain imaging study has recently documented heightened activity of a neural network known to be associated with sustained attention during high-level PVT performance (i.e., fast RTs) and increased activity in a neural default mode network during poor PVT performance (i.e., slow RTs).\textsuperscript{58} Sustained attention in that study and other studies has appeared to be supported by cortical areas of the right middle frontal gyrus and the right in-
Sleepiness as a biologic drive state is assayed using three different general methodologies. Physiologic assays of sleepiness include measures of the rapidity of sleep onset as well as the duration and intensity of sleep. The MSLT is the most standardized and best validated physiologic assay. Sleepiness can also be assayed with a variety of behavioral measures. Since it is believed that increased sleepiness produces state instability during wakefulness, measures that examine sustained waking function are the tasks most sensitive to increased sleepiness. The PVT is the most standardized, validated, and utilized behavioral assay. It is well recognized that, in the presence of moderate to high sleepiness, the behavioral manifestations of that sleepiness many not be evidenced. Examples of this include the patient with sleep apnea who has a mean MSLT latency of less than 5 minutes who shows normal waking function, the emergency room resident who is able to take care of patients despite being on call all night long, and many others. There have been several proposed explanations for this behavioral overriding of physiologic sleep tendency, including motivation, environmental stimulation, and physiologic adaptation. On the other hand, some investigators have hypothesized that the ability to sustain wakefulness is a different drive than sleepiness.69 In fact, the development of the Maintenance of Wakefulness Test was undertaken as an attempt to demonstrate the difference between sleep propensity and the ability to maintain alertness. The results of the present study are the first demonstration of an experimental manipulation (i.e., administration of T8) that differentially impacts physiologic sleepiness relative to measures of ability to sustain waking function. That is, physiologic sleepiness was not prevented with T8-enhanced SWS, as evidenced by no group or group x treatment interactions on MSLT or recovery sleep parameters. On the other hand, measures of sustained attention, as exemplified by the PVT results, were, in fact, spared from the effects of sleep restriction with administration of T8. Whatever causes this dissociation between sleepiness and sustained attention is not clear. However, it can be concluded that it is not mediated by differential awareness of sleepiness (KSS did not differ between groups) or differential motivation (no differential performance on other behavioral measures following sleep restriction). What specific physiologic mechanism allows for normal or near-normal sustained attention in the presence of significant physiologic sleep drive is unclear, but the potential role of SWS in that process is highly intriguing.

It is important to note that we believe these data represent the first systematic experimental dissociation of sleep propensity and sustained attention. Sleep deprivation, sleep fragmentation, sleep disorders, and central nervous system-depressant drugs all negatively impact behavioral, introspective, and physiologic assays of sleepiness.60 Similarly wake-enhancing substances, e.g., caffeine61,62 and modafinil,63,64 improve all three measures of sleepiness in most investigations. Clearly the differential effects of T8, either directly or through its effects on SWS, warrant further investigation.

Most importantly, to our knowledge this investigation is the first to identify behavioral, psychological, and physiologic changes associated with an increase in SWS, regardless of the means with which SWS was enhanced. The potential role of pharmacologic enhancement of SWS in reducing or reversing the effects of sleep restriction deserves significant scientific attention because an effective countermeasure to partial sleep deprivation would be of value in a variety of sustained operations.

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