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EEG Slow Wave Sleep and Slow Wave Activity in Extended Sleep With Bright Light Induced Phase Shifts of Core Body Temperature

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Thesis submitted to the School of Graduate Studies and Research of the University of Ottawa in partial fulfilment of the requirements for the Doctor of Philosophy Degree in Experimental Psychology.

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Now that this has been said, all of you not on my committee don't have to read the rest of the thesis...(Is that a sigh of relief I hear?)...although I encourage you to have a read. It will change your life. Really!

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Curriculum Studiorum

Gregory Christ was born on May 18, 1964, in Ottawa, Ontario. He obtained a B.A. in Psychology from the University of Ottawa in June, 1987, and a M.A. in Cognitive Science from Sussex University in November, 1988.

Abstract

In this study, the time courses of slow wave sleep (SWS) and EEG slow wave activity (SWA) were examined in relation to core body temperature (CBT) during extended sleep periods of 15 hours. This investigation examined the merits of a hypothetical 12-hour rhythm of SWS to: 1) confirm its existence; 2) see if it was reflected by the more objective measure of SWA (power spectral analysis); and 3) determine if there was any relationship between this 12-hour rhythm and the CBT rhythm.

In Study 1, 7 subjects (age 18-22 years) slept in the laboratory for 3 consecutive nights (2 of 8 hours, then 1 of 15 hours). Rectal CBT was monitored during sleep periods. The main findings were that SWS and SWA both significantly increase in the final 3-hour block over the center 3-hour block, and that these late increases were not related to waking after sleep onset (WASO) or rapid eye movement (REM) sleep. Five of the 7 subjects showed a return of SWA, which was defined by the maximum 15 minute running average in the last 5 hours exceeding the same measure for the previous 4 hours (about 2 sleep cycles with lower SWA). With CBT phase defined as the delay from sleep onset to CBT minimum, it was found that late SWS (in the last 3 hours), and magnitude of the SWA return had significant positive relationships to CBT phase.

In Study 2, 3 subjects (age 19, 21, and 29) were studied for 4 series of 4 consecutive nights, with bedtime at 23:30h on all nights. Two series served as baseline (8HBL, and 6HBL). During one series (ML) CBT rhythm was phase advanced using morning bright light (7000-11000 lux, 6:00h-9:00h), and during another series (EL) CBT was delayed using evening bright light (20:00h-23:00h). Subjects were kept in dim light (<250 lux) during these morning and evening periods for the 8HBL and 6HBL. A range of CBT phase to sleep timing combinations resulted, with ML always phase

advanced relative to EL. CBT phase plotted against late SWS and SWA measures showed a positive association between CBT phase and timing of SWA return [except in one subject (#3)], and a smaller positive association to SWA in the last 3 hours [except in one subject (#1)].

When data from Study 1 and the equivalent 8HBL of Study 2 were combined, SWS and SWA late in the sleep period were not significantly related to WASO or REM, and magnitude of the SWA return was statistically significant. There was also a significant relationship between CBT phase and late SWS, magnitude of SWA return , and timing of the SWA return, but not with SWA in the last 3 hours.

The data were consistent with a 12-hour rhythm of SWS and SWA, in which the minor pole does not depend solely on WASO or REM, and is related in timing and magnitude to the CBT rhythm. Magnitude of both poles are likely influenced by prior amounts of waking, but the special conditions of extended sleep illustrate the association of the minor pole to the CBT rhythm.

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List of Abbreviations

6HBL = 6.5 hour baseline series from Study 2.

8HBL = 8 hour baseline series from Study 2.

CBT = Core body temperature (usually rectal).

CMR = Cerebral metabolic rate.

EL = Evening light series in Study 2.

EMG = Electro-myogram.

EOG = Electro-oculogram.

EEG = Electro-encephalogram.

ML = Morning light series in Study 2.

MMPI = Minnesota Multiphasic Personality Inventory.

MSLT = Multiple sleep latency test.

NREM = Non-rapid eye movement sleep.

REM = Rapid eye movement sleep.

SWA = EEG slow wave activity.

SWS = Slow wave sleep.

TST = Total sleep time.

WASO = Waking after sleep onset.

Review of the Literature

SWS Definition and Detection (Scoring)

Sleep has traditionally been divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. This division has been based on variations in electro-oculogram (EOG), electro-myogram (EMG), and especially electro-encephalogram (EEG) signals, recorded on a polygraph, from animals or humans. Sleep has been divided into its various stages by visual scoring of the above measures in 30 second or 20 second epochs, according to standard criteria (Rechtschaffen and Kales, 1968). For the current project, the deeper stages of NREM sleep are of primary interest.

Slow wave sleep (SWS) is made up of the two deepest stages of NREM sleep, stages 3 and 4. Stage 3 is defined by EEG recordings in which at least 20% but not more than 50% of the epoch consists of waves of 2 Hz or slower, which have amplitudes greater than 75 microvolts from peak to peak. Phasic activity like the K-complex, a sharp negative to positive wave exceeding 0.5 seconds, can also be present. Stage 4 is identical except that it contains greater than 50% slow waves per epoch. Another characteristic of SWS is that it tends to decrease over the first 3 to 4 NREM-REM cycles during a normal 8-hour night of sleep, leaving mostly REM and stage 2 toward final awakening.

The divisions between NREM stages 1, 2, 3, and 4 are somewhat arbitrary, being based on visually discernible characteristics, and can obscure much data about changes within and across stages. Stage scoring forces an apparently continuous process into 4 categories, yielding only an interval scale. It has been shown that computer analysis of EEG data can uncover systematic changes not revealed by changes in sleep stage duration or percentage. For example, Borbély, Baumann, Brandeis, Stauch, and Lehmann (1981) studied recovery from 40.5 hours of sleep deprivation and

found peaks in EEG power density during stage 3 and 4 sleep present in all frequency bands up to 7 Hz. Alpha peaks, that are usually scored as waking, were evident mostly in the 9-11 Hz band. High values in the 13-15 Hz band occurred typically in stage 2, seeming to reflect spindle activity. However, they conclude "that effects of sleep deprivation as well as trends within the sleep periods are readily apparent from spectral analysis, but are inadequately reflected by conventional sleep scoring" (p.492). This quote refers mainly to SWS and delta activity (about 0.25 to 4 Hz) during recovery sleep. In their investigation of the time course of slow wave activity (SWA), Brunet, Nish, MacLean, Coulter, and Knowles (1988) found that conventionally scored SWS and spectral analysis were equally sensitive to changes in prior wakefulness, but if extended sleep were allowed, homeostatic regulation of SWS was more evident in data derived from spectral analysis (Akerstedt and Gillberg, 1986a) than from visual scoring (Akerstedt and Gillberg, 1986b). Thus, visual scoring and automatic computerized analysis do not correspond exactly, so these computer techniques may provide more information to clarify previously obscured data.

Theories Of SWS Function

Comprehensive reviews of SWS and its functions are provided by Wauquier, Dugovic, and Radulovacki (1989), and Horne (1988, 1992). Some of this information will be summarized below.

Horne (1989) considers SWS, especially stage 4, to be one of the most important components of sleep, referring to the first 3 REM-NREM cycles, which contain most of an 8 hour night's SWS and hald of nightly REM, as "core sleep." This contention is based on several lines of evidence:

1) After sleep deprivation only about 30% of the total sleep lost is regained during recovery sleep. However, this recovery sleep is typically comprised of all the lost stage

4, about half the lost REM sleep and little or none of stages 1 and 2;

2) In human subjects, when daily sleep time is reduced for several weeks, stages 1, 2 and REM are reduced, but not SWS (Mullaney, Johnson, Naitoh, Friedman, and Globus, 1977);

3) Human SWS is the most difficult type of sleep to deprive (e.g., Agnew, Webb, and Williams, 1967);

4) Natural short sleepers have the same levels of SWS as age matched controls, but have less of other stages (Horne, 1988, p.182).

These characteristics indicate that SWS seems to take priority over other stages of sleep, especially early in a night's sleep, and when sleep is restricted.

One of the main theories about SWS is that it reflects enhanced tissue repair, or restitution, for most organs following the "wear and tear" of use during wakefulness (Adam and Oswald, 1983). The supporting evidence for this view comes from several sources. For example, SWS is related to an increase in human growth hormone (Sassin, Parker, Johnson, Rossman, Mace, and Gotlin, 1969), an increase in cell division during sleep (Fisher, 1968), and that intense exercise during the day leads to increased SWS the subsequent night (Zloty, Burdick, Adamson, 1973). However, Horne (1989, p.111) makes the argument that these lines of evidence are circumstantial[1] and that sleep may

[1]Horne views the evidence of tissue repair as circumstantial in that: a) the hSWS-HGH [human growth hormone] release is more likely to be for the sparing of tissue protein against breakdown, not for increasing tissue growth. It should be remembered that most of us are physiologically in a fasting state during sleep; b) the peaks in cell division are a time-of-day phenomenon not dependent on sleep, but coincidental with sleep; c) exercise effects on sleep are probably an artifact of the accompanying increase in cerebral temperature and metabolism (Horne, 1989, p.111).

provide restitution for the cerebral cortex rather than the rest of the body. Horne contends that physical rest (sitting and standing) is sufficient to facilitate certain tissue restitutive processes, but that this only applies in larger mammals such as humans, carnivores and ungulates that have a cerebral cortex advanced enough to allow relaxed wakefulness.

Sleep deprivation studies also indicate that the primary negative effects of missing sleep are upon the cerebrum (Horne, 1985; Johnson, 1982). Effects mentioned are, for example, cognitive dysfunctions, irritability, lowered threshold for EEG epileptiform activity, and extreme sleepiness. These sleep loss effects are mostly corrected after one period of recovery sleep of about 10-12 hours, during which much of the stage 4 rebound occurs, with the smaller REM rebound not occurring until the second recovery night or beyond. Horne notes that during sleep restriction regimens, psychological performance is not seriously impaired until SWS is restricted, that is when the amount of sleep is less than 5 hours (Wilkinson, 1968).

Another reason why sleep may be necessary for the cerebrum to recover is that, unlike the rest of the body, the cerebrum cannot shut down to any significant extent during waking. Sleep, especially SWS, would provide an off-line period when external stimulation is largely removed so repair or restitution could occur. However, it is still uncertain what if any recovery processes happen during SWS.

Several characteristics of SWS (Horne, 1989, p.113) suggest that this state provides an off-line recovery process: 1) cerebral neuronal firing rates are lowest during stage 4 sleep; 2) of all sleep stages, SWS, especially stage 4, correlates most positively with the length of prior wakefulness (Webb and Agnew, 1971), and in this respect could fit a recovery role; and 3) during SWS the cerebrum

enters into an unusual condition of isolation from both sensory input and from subcortical structures (e.g., Velasco, Velasco, Cepeda, and Munoz, 1982).

One of Horne's main tenets is the link between brain temperature and subsequent SWS amounts. Artificially raising body (i.e. cerebral) temperature during the daytime actively by exercise, or passively by sitting in a warm bath, leads to SWS increases during the subsequent night (Horne and Staff, 1983; Horne and Reid, 1985). However, if subjects are force-cooled during exercise to reduce core (i.e. cerebral) temperature increases, SWS does not increase (Horne and Moore, 1985). Horne theorizes that raised cerebral temperature is associated with increased cerebral metabolic rate (CMR), which initiates the SWS increases. Increasing CMR by raising sensory stimulation also leads to elevations in SWS (Horne and Minard, 1985), and SWS positively correlates with thyroid activity levels (Ruiz-Primo et al., 1982) possibly also due to CMR changes. These SWS increases could result because raising CMR may cause more cerebral "wear and tear" and an increased need for cerebral restitution, or an accelerated build-up of SWS promoting substances in the brain. (There are several candidates for a SWS promoting substance, for example prostaglandin; Inoué et al., 1984).

There are other theories relating brain temperature to SWS not so much for the restorative functions that Horne proposes, but simply for thermoregulation and energy conservation. These theories and their supporting evidence, some of which has already been mentioned, will be covered later.

It has also been suggested that SWS is related to enhancement of the immune system (Moldofsky, Lue, Eisen, Keystone, and Gorczynski, 1986; Krueger, Walter, and Levin, 1985). However, it is unclear whether this increase is to

maintain or bolster the immune system for general health, or if it is to provide protection during the increased vulnerability of the lower body temperature of SWS.

Timing of SWS

The timing of SWS is an important factor in determining the function of SWS. Firstly, it has been observed that there appears to be a fixed amount per day of SWS, especially stage 4, which can be distributed over a nap and the subsequent night's sleep without affecting total sleep time at night (Feinberg et al., 1985). Apparently an afternoon nap can use up some of that night's stage 4 sleep. Thus SWS appears to have some fixed daily requirement (quota?) that can be fragmented, but that must occur.

There is much evidence to suggest that prior wake time is a key determinant of subsequent SWS amounts. This relationship of SWS to prior wakefulness is summarized by Webb (1989). It has been observed that the amount of SWS decreases as time asleep increases (e.g., Williams, Agnew, and Webb, 1964), and that longer periods of wakefulness before sleep lead to more stage 4 sleep (Webb and Agnew, 1971). From these observations have come more exact descriptions of this relationship. Citing experiments using abnormal sleep schedules (Hume and Mills, 1977) and the computer based studies of Borbély (1982), Knowles, MacLean, Salem, Vetere, and Coulter (1986) conclude "that SWS increases exponentially as a function of prior wakefulness and decreases exponentially during sleep. The equations account for 91% and 96% of the variance, respectively." Horne (1988, p.197) estimates this relationship to be more linear at approximately 6.5 minutes of SWS for 1 hour of wakefulness or REM, since Horne's theory sees REM and waking to cause about the same amount of cerebral "wear and tear." Webb (1989) agrees that SWS has generally been shown to be independent of circadian time of sleep onset, but that REM

sleep does have circadian patterns that may prevent (suppress?) SWS at certain times.

Two Process Model

Borbély (1982; 1984, chapter 12) outlined a theory relating prior wakefulness to SWS using a two process model. In this model, there is a "Process S" which indicates sleep propensity during waking, and "depth" of sleep while asleep. The level of process S rises exponentially during waking and falls during sleep. The other "Process C" corresponds to a circadian rhythm of sleep propensity, which is independent of prior sleep or waking, and is highest at 4:00h and lowest at 16:00h. Since Process S rises with waking and declines with sleep, it may correspond to oscillations in the level of an endogenous sleep substance, or hypnotoxin. Process C would reflect an "internal clock", which could be located in the suprachiasmatic nuclei, which may regulate other rhythmic processes like core body temperature (CBT). This is a single oscillator model, although some consider Process S to be a second oscillator (Strogatz, 1987). Since SWS is much more affected by prior wakefulness than are other sleep stages, Process S primarily predicts need of SWS, with REM being controlled more by circadian influences. Process C can be depicted as a rhythmically fluctuating upper and lower boundary, with Process S between the two, building up during waking until levels reach the upper limit of C, when sleep is initiated; after this, Process S decreases until reaching the lower limit of C, when sleep is terminated, allowing S to rise again (Daan, Beersma, and Borbély, 1984, p. R163). These authors acknowledge that S decreases may just occur during NREM, with REM sleep not affecting, or perhaps increasing Process S, as Horne believes it would.

The 2-Process Model views SWS as having no circadian component, and solely being a function of prior wakefulness. Support was recently provided by Dijk, Beersma, Brunner,

Daan, and Borbély (1990) in their study of computer analyzed SWA in subjects in various circadian phases. During daytime naps, daytime recovery sleep after sleep deprivation, and phase advanced sleep (i.e. early bedtime), SWA decreased with time asleep, independent of the circadian phase. Also, levels of SWA were related to amount of prior waking. Thus SWA occurred as Process S would predict.

An updated version of the 2-Process Model has been developed (Achermann and Borbély, 1990) to include ultradian features of sleep that were not dealt with in the original formulation, like the NREM-REM cycle, SWA changes within NREM episodes, and increasing duration of consecutive REM periods. An oscillator that triggers REM sleep every time it exceeds a certain threshold has been added. In this version of the model, the decay of Process S is proportional to the momentary level of SWA, and Process S can build up at all times, even during sleep (Achermann, Beersma, and Borbély, 1990). With this revised model, it seems that after the initial termination of SWS in the first part of the night, perhaps Process S could build up sufficiently during extended sleep to cause a resurgence of SWS at some point.

Models of Sleep Timing

There are also several models of human sleep-wake rhythms using at least two oscillators. Strogatz (1987) briefly reviews and compares several of these models. They are based mostly upon data from free running rhythms of subjects in time free environments. In the absence of external timing signals (zeitgebers), the rhythms of CBT and sleep-wake, which usually have a stable phase relationship to each other, can uncouple and each proceed at its own frequency. This is known as "internal desynchronization." However, most of these models deal only with the timing of sleep and waking, and do not look at the timing of specific stages of sleep, like stage 4, except the 2-Process Model of

Daan, Beersma, and Borbély (1984) described previously.

A relevant example is the 2-Oscillator Model, described by Moore-Ede, Sulzman, and Fuller (1982), and mathematically modeled by Kronauer, Czeisler, Pilato, Moore-Ede, and Weitzman (1982). In this model, there is an X pacemaker, that times certain rhythms like those of REM sleep, CBT, plasma cortisol concentration, and urinary potassium. In addition, there is a Y pacemaker that drives the rest-activity cycle and the rhythms of SWS, skin temperature, plasma growth hormone concentration, and urinary calcium excretion. The X and Y pacemakers are coupled together to keep a steady circadian rhythm, however each oscillator has its own frequency, which can be observed during internal desynchronization. It appears that the coupling strength of X on Y is about 4 times greater than that of Y on X (Kronauer et al., 1982). It was further postulated that external stimuli that entrain these oscillators to the 24 hour day can only influence the X, or "deep", pacemaker through effects upon the Y pacemaker. However, it has been demonstrated that the X pacemaker can be directly affected by light (Czeisler et al., 1986), so this model had to take this finding into account (Kronauer, 1987a) by allowing X to be influenced by changes in light intensity. Concerning the timing of SWS, according to this model, it would seem that core body temperature (controlled by X) is related to REM sleep and could influence SWS (Y) only by the coupling between the two oscillators. Thus one would expect a sudden shift in body temperature to perhaps reduce SWS at certain times due to a pressure for REM sleep, but not to shift SWS rhythms per se.

Due to the evidence of a 12 hour rhythm of sleep propensity, to be discussed below, Kronauer (1987b) has proposed to split the weak Y oscillator into two weak Y1 and Y2 oscillators to incorporate these data.

12-Hour (Circasemidian) Rhythm of SWS

In contrast to the 2-Process theory, in which SWS is solely a reflection of prior waking, Broughton (1975, 1988) has proposed that there is a circasemidian, or twice daily, rhythm of pressure for sleep and SWS. Evidence of a 2/day sleep propensity comes from many sources:

> The mid-afternoon is usually the timing of: the last nap given up in growth and development; the so-called "post-lunch dip" in performance of awake subjects; voluntary naps of both adults (especially frequent in college students) and the retired and elderly; the siesta of cultures with typically reduced night sleep; shortened daytime sleep latencies on the Multiple Sleep Latency Test (MSLT) in normals and in sleep disorder patients with excessive daytime sleepiness; and sleep attacks and voluntary naps in narcoleptics, as confirmed by sleep logs (Bastugi and Jouvet [1985]) and by either in-lab (Billiard et al. [1986]) or ambulant home (Broughton et al. [1986]) recordings. There is an equivalent peak in industrial accidents and in deaths, both of which show a similar 2/day distribution. [Broughton, 1988, p.41]

Accompanying this mid-afternoon sleep propensity, approximately 12.5 hours after the first onset of SWS the previous night, is a pressure for SWS. Webb (1971) found that naps occur most frequently in mid-afternoon, and also most frequently have SWS at that time. Also, in environments lacking time cues, when subjects are allowed to nap or do so against instructions, sleep both free-runs and splits into a bimodal distribution. Typically a major sleep episode occurs at the time of the circadian minimum of core body temperature, and a minor sleep episode (nap) about 180 degrees out-of-phase (Zulley and Campbell, 1985).

Zulley and Campbell (1989) have more recently studied sleep architecture of subjects in a "disentrained" environment with instructions to sleep any time they wanted. Again, a major sleep episode occurred around the CBT minimum and a minor one near the CBT maximum. However, because of

the variability of when subjects napped, it was possible to look at the relationship of prior waking time to SWS content of nap sleep. They found that:

> Those sleep episodes that began within 4 hours of the maximum in core body temperature contained significantly more slow wave sleep than did all other daytime sleep periods, approximating proportions typical of nocturnal sleep. Multiple regression analysis revealed no relationship between measures of slow wave sleep and prior wakefulness" [p. 580].

They go on to state that these data "complicate the presumed strict relationship between the buildup of SWS propensity and prior time awake and they suggest the need for a circadian component in characterizing this process of sleep regulation." (Campbell and Zulley, 1989). These results run counter to the 2-Process Model, and that of Horne. The amount of SWS was also not related to nap duration, but to proximity of the nap to CBT maximum, implicating CBT as a determinant of SWS.

Broughton (1988) speculated that sleep onset both resets the rhythm of CBT with a further decrease, and also initiates the mechanism for SWS which phase-sets the first major SWS pulse, and the minor SWS pulse some 12.5 hours later. He also acknowledged that the degree of SWS pressure for both circasemidian poles mainly reflects prior wakefulness, indicating that the preceding waking behaviour so important to the 2-Process Model is taken into account in this view.

Extended Sleep Paradigm

During the 1970's, in studies involving long sleep episodes it had been observed that there was an "apparently reliable presence of a stage 3/4 'kick' in very extended sleep" (Webb, 1978). This SWS resurgence would provide support for Broughton's proposal. To systematically test this SWS return, Gagnon and De Koninck (1984) had 6 (of 8)

subjects successfully extend their sleep for 15 hours (after 2 adaptation nights of approximately 8 hours each) to observe whether SWS did return in the absence of any waking for Process S to build up. They found a significant SWS return after 12 hours. Later analyses confirmed that, although there was some waking after sleep onset (WASO), this and/or REM sleep amounts were unrelated to the duration of the SWS return (Broughton, De Koninck, Gagnon, Dunham, and Stampi, 1990).

To further test whether this return of SWS showed other characteristics of a biological rhythm, Gagnon, De Koninck, and Broughton (1985) used a paradigm with extended sleep and a phase delay in bedtime. Ten subjects, after spending two 8-hour adaptation nights in the laboratory, were tested during extended sleep with normal bedtime (midnight) to observe the return of SWS. Then one week later, the same 10 subjects returned to the lab for one night of 7-8 hours starting at midnight, followed by an extended night phase delayed to begin at 4:00h. Eight of the 10 subjects were able to extend their sleep beyond 12 hours. The results showed two returns of SWS, one at the same time of day (12:28 +/- 33.59 min) as had occurred with sleep onset at midnight, and a second 13 hours and 32 minutes after the first appearance of SWS. Thus it appears that the SWS return 12.5 hours after the habitual bedtime of midnight persisted, but was also accompanied by a new return 13.5 hours after the new bedtime. To clarify this mixed SWS pattern, 10 new subjects were studied with bedtime moved to 4:00h but on 4 consecutive nights of 7-8 hours, so the subjects could habituate. The fourth night was an extended night. Six of the 10 subjects managed to extend their sleep. In the extended sleepers, SWS returned 12 hours and 24 minutes after its first appearance. Thus from these studies, it appears that SWS tends to return about 12.5 hours after its

first onset, and that it can be phase delayed by manipulating initial sleep onset. It was also demonstrated that the midday SWS tendency persists at the usual time of day for at least one day after a sudden delay in sleep onset. These findings support the idea of a 2/day biological rhythm of SWS that can be reset by manipulating onset of the major sleep episode. This result is difficult to explain using the original 2-Process Model (Daan, Beersma, and Borbély, 1984), that would not predict either SWS return except by WASO or WASO+REM, which was not the case. The modified 2-Process Model (Achermann and Borbély, 1990) allows for Process S to build up during sleep, which may result in a return of SWS after sufficient extended sleep, but it would not explain why there was a SWS return phase-locked to the habitual bedtime even when the new bedtime would have completely changed the course of Process S.

However, these studies by Gagnon and De Koninck (1984) and Gagnon, De Koninck, and Broughton (1985), and another study finding evidence of a SWS return in extended sleep (Webb, 1986), used solely visual scoring of EEG, which yields only an interval scale. More objective and detailed computer analysis techniques could be used to address the same questions. Dijk, Brunner and Borbély (1990) have studied the time course of EEG spectral power density during extended sleep. In this study, 9 subjects slept for two baseline nights in the laboratory (23:00h to 7:00h), then were sleep deprived for an entire night (36 hours waking) before going to bed the next night at (19:00h until at least 7:00h). This sleep deprivation and early bedtime was done to reduce WASO which would disturb the course of Process S during sleep. They found the expected decline in SWS or of SWA (reflected in spectral power density) as time asleep increased, but no evidence of a return in SWS or SWA. However, there are some problems comparing this study to the

work above of Gagnon and colleagues.

By using sleep deprivation, Dijk, Brunner and Borbély (1990) have influenced the subsequent sleep of their subjects. They observed the expected SWS rebound early in the sleep episode with increased SWS and higher power densities in the first two cycles relative to baseline. But what does this do to subsequent sleep in an extended paradigm? It has also been documented that REM sleep rebounds after sleep deprivation, especially in the second night of recovery sleep. With extended sleep, is this REM rebound experienced in the extended portion of the recovery sleep? If so, this would perhaps mask the smaller second peak of SWS. Also, Dijk et al. used a sudden phase advance of sleep onset. If the timing of the second SWS peak were rigidly set by only sleep onset, one might expect the return to occur 12.5 hours after such a phase advance. However, during the phase delay performed by Gagnon, De Koninck and Broughton (1985), there was still a minor peak at the time of day of the original SWS return, in addition to the newly emerging one set by sleep onset. By choosing 19:00h for sleep onset, subjects are not adjusted to this time for sleep onset for any of their biological functions, and subjects' sleep is not examined during the time of day when the habitual second SWS peak is already set (approximately 13:00h). Thus one would expect to see only a moderate return of SWS at best with such a protocol.

Extended Sleep and Core Body Temperature (CBT)

One way to further examine the possibility that there is a second SWS peak, and to examine if the two peaks behave as a 12-hour biological rhythm, is to follow the same extended sleep protocol as Gagnon and De Koninck (1984), but to monitor and manipulate other biological rhythms that are likely to be related to the postulated SWS rhythm and observe the effects, without changing the timing of sleep.

According to the previously cited study of Campbell and Zulley (1989), a biological rhythm probably related to the circasemidian appearance of SWS is the daily fluctuation of CBT.

Dijk, Cajochen, Tobler, and Borbély (1991) performed an experiment in which 8 subjects spent 3 nights in the laboratory (2 from 24:00h to 7:00h, and the last from 24:00h to 15:00h), with rectal temperature being measured during sleep periods. EEG was both visually scored and spectral power analyzed. Regarding a reappearance of SWS or SWA, the authors report that "In hours 12-15, %SWS and SWA in NREM were slightly higher than in the preceding interval. This increase was, however, not significant" (p.299). Concerning CBT (T_{core}), Dijk and colleagues (1991) found "T_{core} decreased during NREM sleep at the beginning of sleep, and the rate of decrease of T_{core} within NREM episodes was positively correlated with SWA. However, in the second part of sleep, no consistent relation between the rate of change in T_{core} and SWA was observed, and T_{core} even increased during NREM sleep" (p.305). The article concludes that the time course of SWA was primarily sleep dependent and different from the course of CBT which was under circadian control.

The data of Dijk et al. (1991) and those of the previous extended sleep studies are quite similar, but the discrepancy between interpretations may be due partly to the fact that Dijk et al. included the data of one subject who was not able to extend his sleep while Gagnon and De Koninck (1984) excluded 2 unsuccessful subjects. Both data sets show that there is a resurgence of SWS in most, but not all, subjects who extend their sleep to between 12 and 15 hours, and that this SWS resurgence does not reach levels as high as those at the beginning of sleep.

The CBT findings of Dijk et al. (1991) show that if

there is a relationship between SWA and thermoregulation, it is not a straight-forward one.

SWS and CBT: Thermoregulation

Sewitch (1987) reviews the literature relating CBT to SWS, especially the CBT drop at sleep onset. Gillberg and Akerstedt (1982) have shown that a rapid decrease in rectal CBT is related to SWS in humans, which persists for up to 2 hours, after which CBT returns to the expected level in the circadian variation. Sewitch, Kittrell, Kupfer, and Reynolds (1986) have demonstrated that "driving" rectal CBT down at sleep onset is associated with increases in Stage 4 SWS and lengthening first NREM-REM cycle. A fall in CBT accompanies sleep onset in humans regardless of where it intersects the daily CBT rhythm (Gillberg and Akerstedt, 1982). This study also showed that total sleep time (TST) was more related to the rhythm of CBT (i.e. longer sleep tended to begin when CBT was high and falling, and sleep tended to terminate when CBT was rising), than it was to prior wakefulness, even when involving sleep deprivation of up to 40 hours. The 2-Process Model would predict a strong relationship of prior wakefulness to total sleep time, but mostly to SWS time, and SWS amounts were not reported in this study.

As mentioned previously, raising CBT either passively (through warms baths; Horne and Reid, 1985; Jordan, Montgomery, and Trinder, 1990) or actively (through exercise; Horne and Moore, 1985) led to greater amounts of SWS. After studying 7 days of passive body heating, Di Nisi, Ehrhart, Galeou, and Libert (1989) concluded that "SWS, and particularly stage 4 sleep, is a state in which specific thermoregulatory changes occur...This conclusion is reinforced by the observation that sweat gland activity is particularly enhanced in SWS (Sagot et al., 1987)" (p.143). Berger, Palca, Walker, and Phillips (1988) found that in each of 4 male subjects, rectal and tympanic temperature at

SWS onset had a positive correlation to mean total minutes of SWS in the first 7 hours of an 8 hour night. Higher CBT at sleep onset was associated with steeper declines in CBT during SWS. They speculate that SWS may be related to thermoregulation, more specifically to reducing CBT, perhaps for energy conservation. They also conjecture that the return of SWS in the extended sleep studies of Gagnon and De Koninck (1984) and Gagnon, De Koninck and Broughton (1985) may be due to the circadian rise in CBT at the time of the return. However, as mentioned earlier, Dijk et al. (1991) found no consistent relationship between SWA and CBT.

In a study of sleep and hypothalamic centers that control CBT in the cat, Szymusiak and McGinty (1990) concluded that "hypnogenic and thermoregulatory responses are closely integrated and that heat-sensing mechanisms normally drive SWS" (p.55). Also, when they manipulated brain temperature in the chronic cerveau isolé cat, sleep occurred during warming (39.5 C). Thus it appears not only that SWS is driven by elevated brain temperature, but that peripheral input is not required for this process, which is mediated in the preoptic area of the anterior hypothalamus. "We suggest that heat loss is also the long-sought function of mammalian SWS" (p.58). They speculate that there may be two mechanisms for SWS: one related to heat exposure, and one related to low absolute brain temperature.

Thus it may be that SWS/SWA is related to regulation of brain temperature, and that CBT may only be indirectly related to this.

However, Beersma and Dijk (1992), using acoustic stimulation, suppressed SWS by 58% in 8 male subjects (mean age 49.8 years), and found no significant change in the course of rectal CBT from baseline or recovery sleep. But since aging is associated with attenuated circadian amplitude of CBT change, and also lower amounts of SWS,

these subjects are not ideal for the study of the relationship of SWS to thermal downregulation. Nevertheless, the results indicate that the CBT rhythm is not significantly disturbed if just over half of SWS is missing. This finding is difficult to reconcile with the previous work of Szymusiak and McGinty (1990), but discrepancies may be due to brain versus core temperature differences, as Beersma and Dijk (1992) point out. Perhaps a replication of the Beersma and Dijk study using younger subjects (early 20's) and also monitoring brain temperature could clarify the issue.

SWS as an Energy Conservation Process

Berger and Phillips (1990) review evidence that SWS serves a major role in energy conservation. In small mammals, hibernation and torpor both involve large decreases in CBT, up to 30° C (Walker, Glotzbach, Berger, and Heller, 1977) and 20° C (Berger and Phillips, 1988) respectively, with EEG slow waves being a prominent feature of both these states (at CBTs above 25° C). When fasting, average CBT drops and the nocturnal drop in CBT is even more pronounced, which saves energy. An interesting finding by Phillips and Berger (1989) was that when pigeons were exposed to constant light with free access to food and water, the CBT rhythm along with SWS and REM sleep all disappeared and were replaced by waking alternating with periods of drowsiness. However, there was no compensatory recovery of sleep after the pigeons were subsequently exposed to constant darkness or a 12 hour light/12 hour dark schedule. This runs contrary to restorative theories of sleep function (i.e., no SWS rebound after very extended waking).

In large birds during fasting (Dewasmes, Buchet, Geloen, and Le Maho, 1989) and humans after 2-3 days of fasting (MacFadyen, Oswald, and Lewis, 1973), there are increased durations of SWS but without change in nocturnal

CBT. Berger and Phillips (1988) conclude that increased length rather than depth of circadian decrease in metabolic rate may be an effective energy conservation strategy for large endotherms with small surface-to-volume ratios and low thermal conductance (p.47 of Berger and Phillips, 1990).

In further support of the link between SWS and brain temperature it was found that by manipulating brain temperature during sleep, by heating or cooling the face, SWS was significantly greater on heating nights than on cooling nights, while other sleep stages and waking were not affected. Also, SWS was strongly correlated to tympanic temperature, but not with rectal temperature (Berger and Phillips, 1988; Morairty, Phillips, and Berger, 1988).

The above information tends to support the idea that there are brain mechanisms, likely in the hypothalamus, that can directly detect brain temperature, and subsequently control SWS onset to reduce this temperature. There is also the possibility of another mechanism that can detect low brain temperature and also initiate sleep onset.

Determination of CBT Phase

CBT minimum has often been used as the phase marker for the CBT rhythm, but the system is responsive to effects of non-systematic activity, light, and sleep which may "mask" the true CBT phase. One way to diminish these masking effects has been the use of a constant routine procedure (see Czeisler et al., 1985), during which subjects are kept awake in constant conditions for 40 hours, beginning at habitual waking time. Factors held constant include posture (supine wakefulness), light (about 150 lux), food intake (daily calory intake is divided into equal hourly amounts), and social contact (always a person present to keep subject awake and administer tests at equal intervals). Subjects' EEG is also monitored to detect if any sleep occurs. The 40 hour period ensures that at least 1 CBT minimum will occur

not within 5 hours of awakening, so that the masking effect of sleep on CBT would be ruled out (Czeisler et al., 1989). This procedure also appears to have no phase shifting effect on the underlying pacemaker controlling rhythms like that of CBT (Czeisler et al., 1989).

For the purposes of the current studies, the sleep deprivation of a constant routine was considered problematic. The current studies sought to examine the 12-hour rhythm of SWS without the potentially confounding situation of recovery after sleep deprivation. However, use of a constant routine in future research of this nature is highly recommendable. In the current studies, the CBT phase was determined by the CBT minimum during the extended sleep period, which would provide constant conditions of sleep unless there was much WASO early in the night. There was also an attempt to control levels of activity (i.e., no strenuous exercise), and light exposure (instructions to avoid outdoor light while outside the laboratory), which were verified by ambulatory monitoring. These compromises were made to ensure prior waking and other conditions were as normal as possible prior to the extended sleep.

CBT Manipulation by Bright Light

It has been demonstrated that biological rhythms in animals can be manipulated by exposure to bright light (for review, see Moore-Ede, Sulzman, and Fuller, 1982). However, the relationship of light to the circadian rhythms of humans has been less thoroughly mapped out. Nevertheless, there is research indicating the various effects that certain light intensities presented at various times of the circadian phase can have upon human biological rhythms. In general, light must be above a certain intensity to influence the human circadian system. Estimates run from 1500 to 2000 lux (Lewy, Wehr, Goodwin, Newsome, Markey, 1980; Wetterberg, 1980), to 2500 lux (Honma, Honma, and Wada, 1987) as

necessary in order to suppress the level of nocturnal melatonin. Wever (1985) and Wever Polasek, and Wildgruber (1983) found that several hours of exposure to 4000 lux light extended the limits of entrainment to periods longer than possible with just the social influence of dimmer lights alone. Such studies have led to refinements in the various models of circadian rhythms and sleep.

For the study of a 12-hour rhythm in SWS that is linked to CBT, this review will center on the effects of light upon sleep and CBT. For our purposes, we seek to change the phase relationship of CBT to sleep such that the extended sleep occurs at the same clock time (i.e., same amount of prior wakefulness), but that CBT is phase advanced or delayed to observe what, if any, changes occur to the sleep structure and return of SWS.

Czeisler et al. (1986) have shown that the circadian clock, as measured by CBT and cortisol secretion rhythms, can be shifted by light without altering the sleep-wake cycle. One female subject (66 years old), with a slightly phase advanced rhythm of CBT, was exposed to bright lights (7000-12000 lux) from 19:40h to 23:40h each evening for 7 days. Fifteen minutes of intermediate level light (3000-6000 lux) preceded and followed each 4-hour exposure. A 5.7 hour phase delay shift in CBT minimum was evident 1 to 2 days after the light treatment began, as was a 6 hour delay of serum cortisol levels. These findings are important in that bright light can shift certain biological rhythms independent of the sleep-wake cycle. Unfortunately, this study is of only one subject, and sleep structure was not monitored. Thus even though total sleep time may have stayed the same, the amount of each stage or normal NREM-REM cycle may have been disturbed.

Drennan, Kripke, and Gillin (1989) studied the effect of 3 evenings of bright light versus dim light exposure. Ten

subjects were exposed to either dim lights (300 lux) from 18:00 to 23:00 h, or bright lights (3800-6000 lux) from 18:00 to 21:00 h on the first evening, then 18:00 to 23:00 h for the last 2 evenings. They found that the bright lights phase delayed CBT 1.5 to 3 hours, depending upon night of study, and that sleep latency was delayed only about 15 minutes. This finding suggests that the model of Kronauer, Czeisler, Pilato, Moore-Ede, and Weitzman (1982) is incorrect in that it is unlikely that the strong X oscillator (CBT, delayed 1.6-3 hours) was phase shifted entirely through effects on the weak Y oscillator (sleep, delayed 9 minutes). According to this model, one would expect a prompt effect on Y (sleep) to produce a gradual change in X (CBT), while the opposite was observed. These data correspond better to a model presented more recently by Kronauer (1987a) in which synchronizing effects influence primarily the X oscillator (CBT). The 2-Process Model agrees with these data in that the Process C (reflected by CBT) is influenced directly, and sleep-wake changes would follow as a result of this modified threshold.

Regarding changes to sleep structure that result from evening bright light, EEG SWA (0.5-4.0 Hz) has been observed to increase with a single 2 hour light pulse (2500 lux) over a dim light baseline. This increase lasted until the end of the second NREM period, although changes in SWS were non-significant (Bunnell, Treiber, Phillips, and Berger, 1992).

In a study performed by Dijk, Beersma, Daan, and Lewy (1989), 8 male subjects were exposed to either bright light (2000 lux) or dim light (1 lux) between 6:00 h and 9:00 h for 3 consecutive days. The result of the bright light was a phase advance in the evening rise in plasma melatonin and in time of sleep termination. The sleep reduction was at the expense of REM sleep. EEG power densities were not affected between 0.25 and 15.0 Hz during REM or NREM sleep. If sleep

termination is defined as the first 15 minutes with no stage 2, 3, 4, or REM sleep, sleep duration was reduced an average of 54 minutes after the bright light treatment. Time spent in stages 3 and 4 was virtually identical for the 2 conditions. REM was reduced.

Another study by Dijk, Visscher, Bloem, Beersma, and Daan (1987), found that in 8 male subjects exposed to dim (1 lux) or bright (2000 lux) light in the morning (6:00h-9:00h) on 3 consecutive days preceding sleep assessment, the time course of EEG energy was not affected by light treatment. However, after bright light there was an earlier rise in CBT (phase advance of approximately 1 hour), and sleep duration was significantly shorter. Also, in this study bedtime was 2 hours later on the assessment night than on the treatment nights.

Although a detailed phase response curve for humans to bright light was not found in the literature, there are theoretical (Lewy et al., 1983), and preliminary empirically based models (Dawson, Morris, and Lack, 1989; Czeisler et al., 1989). From these models and the above evidence, morning light appears to phase advance CBT, but also shorten total sleep time by earlier awakening, while evening bright light appears to phase delay CBT. If CBT rhythm is related to a 12-hour rhythm of SWS/SWA, then shifting the CBT rhythm relative to sleep onset should shift the SWS/SWA return in the same direction. However, for the study of extended sleep, there is the problem that phase advancing CBT may induce shorter sleep (i.e., waking up too early and having trouble falling back to sleep), which would contaminate findings about the SWS/SWA return.

The original 2-Process Model would relate a SWS return only to prior WASO or REM. The revised 2-Process Model would predict much the same, except that a SWS return may be possible after sleep extended enough to build up Process S.

Shifting CBT should have no effect on a SWS return according to either version of the 2-Process Model, unless it affects WASO or REM. Thus phase advancing and phase delaying CBT, then observing SWS and SWA changes in subsequent extended sleep, with a standard bed-time, should clarify some of the relationships between SWS or SWA with prior WASO, REM, and CBT. The studies outlined below examined these relationships.

Description of the Current Studies

Study 1 (preliminary report in De Koninck, Christ, Carrier, Hébert, and Fortier, 1990) sought in part to replicate the work of Gagnon and De Koninck (1984) and Gagnon, De Koninck and Broughton (1985), that there is indeed a return of SWS about 12.5 hours after first SWS onset, and also to analyze the data using power spectral analysis. Power spectral analysis gives a more objective measure which is hypothesized to reflect the course of Process S more closely than visual scoring when extended sleep is involved (Brunet, Nish, MacLean, Coulter, and Knowles, 1988). Further, following the previously mentioned evidence of a link between CBT and SWS, rectal CBT was monitored. A relationship between the rhythm of CBT and the 12-hour rhythm of SWS (Broughton, 1975; 1988) was sought. In the subsequent exploratory Study 2, the CBT rhythm was phase advanced using bright light in the morning, and phase delayed using evening bright light, while bedtime (i.e., prior waking) was held constant. This was done, again, to indicate if the 12-hour rhythm of SWS exists, and if the SWS rhythm could be phase shifted by manipulating CBT, since it was shown to shift in response to time of sleep onset (Gagnon, De Koninck, and Broughton, 1985). These manipulations would also show if SWS was related primarily to the CBT rhythm (Kronauer's X pacemaker), or to other factors.

The protocols below were examined and passed by an ethics committee at the University of Ottawa.

Study 1

Hypotheses

1) There should be a 12 hour rhythm of SWS/SWA pressure, such that SWS/SWA should return 12.5 hours after sleep onset in extended sleep. Since this should be a biological rhythm, the amount of SWS/SWA in the return should be independent of the amount of intervening WASO, REM, and WASO+REM.

2) There should be a relationship between CBT rhythm and SWS/SWA.

Predictions

1) There should be a return of EEG SWS (detected by visual scoring) approximately 12.5 hours after sleep onset. This return of SWS should be unrelated to intervening WASO, REM or WASO+REM sleep amounts.

2) There should be a similar return of SWA (as measured by spectral analysis) after 12.5 hours, also not related to WASO, REM or WASO+REM sleep.

3) There should be a relationship between CBT and magnitude of the SWS/SWA return. Either circadian phase of CBT, or perhaps magnitude of CBT change, should be related to SWS/SWA return. More specifically, the CBT rhythm should have a stable phase relationship to the postulated 12-hour rhythm of SWS/SWA. Consequently, CBT phase should have a positive relationship with the SWS/SWA return magnitude and timing because a) sleep onset occurring closer after the CBT maximum starts to decline (i.e., a long delay to CBT minimum) should promote longer sleep episodes (Gillberg and Akerstedt, 1982) so the minor pole of the 12-hour rhythm may be observed with less sleep disruption; b) longer delays to CBT minimum should allow a longer period between initial sleep onset SWS/SWA and the minor pole so that they do not appear as continued SWS/SWA as opposed to diminishment then

return of SWS/SWA; and c) greater delay to CBT minimum should mean greater CBT change during sleep (drop and rise), which could promote late SWS/SWA for thermoregulatory reasons.

4) Presuming that SWS/SWA plays some role in thermoregulation, the reappearance of EEG SWA will be accompanied by a drop in body temperature.

Method

Subjects

Ten subjects (3 male, 7 female; aged 18-22 years) were selected for their ability to extend their sleep, as indicated by a sleep habits questionnaire. They were then interviewed to screen for any medical or psychological problems and completed a Minnesota Multiphasic Personality Inventory (MMPI). The MMPI results showed that all subjects were within normal ranges on all scales (see Appendix 1). Since this was a screening tool only, no further analysis was done with MMPI data. None of the subjects took drugs or medication, and they were instructed not to nap, engage in strenuous exercise, or consume alcohol or caffeine during testing periods. Testing was scheduled to be not within 4 days of menstruation for female subjects. Subjects were paid $75 for their participation.

Design

Subjects slept for 3 consecutive nights in the laboratory. Each subject was alone in a windowless, sound attenuated room during sleep recording. The first night served as adaptation as well as screening for sleep disorders. The first 2 nights were of 8 hours, with bedtime as close as possible to the subjects' habitual bedtimes, but always between 23:00h and 1:00h. The final night commenced at the same bedtime, but subjects attempted to sleep for 15 hours until the next afternoon (on a Saturday in all cases).

Measures

Standard polysomnographic measures, EEG, EOG, and EMG, were recorded continuously every night (Rechtschaffen and Kales, 1968). EEG was recorded from C3 and C4, referenced to linked mastoid sites. (Linked mastoids were used to allow study of interhemispheric activity in future). These measures were recorded using Grass gold cup electrodes, and a Nihon Koden (EEG-4314B) polygraph, and were simultaneously recorded onto paper and magnetic tape using a Vetter Digital PCM recording adapter (Model 4000A) amplifier and a video cassette recorder (JVC HR-D750U). The polygraph was calibrated to 7mm/50μV, with paper speed at 10mm/sec.

EEG, EMG, and EOG signals were computer analyzed using a personal computer (486 class) and an FFT routine provided by Rhythm and Eclipse software (Stellate Systems). The signals were digitized at a sampling rate of 128 Hz from the magnetic tape. Signals were low pass filtered at 35 Hz. The EEG signals were analyzed in 4 second epochs, and integrated spectral power densities were calculated. Data from 5 consecutive epochs were averaged into 20 second epochs and values were collapsed into the following frequency bins: Delta = .75-4.5 Hz; $Delta_{Low}$=.75-2.5 Hz; $Delta_{High}$= 2.5-4.5 Hz; Theta= 4.5-8.0 Hz; Alpha= 8.0-12.75 Hz; Beta= 13.0-20.25 Hz. Twenty second epochs with artifact, usually due to movement, were identified visually and rejected from further analysis. The same 20 second epochs were visually scored according to Rechtschaffen and Kales (1968).

CBT was measured while in bed, using a rectal sensor (YSI model 4018912907) inserted about 12cm into the rectum, and was recorded on a personal computer every 20 seconds using software developed at this lab. A constant routine procedure would have provided a more reliable way to determine circadian phase of CBT than simply CBT while asleep, but the scheduling of a constant routine prior to the extended sleep seemed impossible without disrupting the

prior wakefulness requirements of the protocol (i.e., no sleep deprivation), and if given soon after the extended night, the long sleep could have changed the circadian phase, contaminating that measure. Thus a constant routine was seen as not a possibility for this experiment.

Results

For analysis, the extended portion of the data was considered to be the final 5 hours of sleep, since a normal sleep episode would terminate in 10 hours or less (in general and for all of the subjects in this study). The final 3 hours were of special importance because this was beyond 12 hours. Data were not analyzed by NREM-REM cycle because by the extended portion of sleep, this cycle becomes disrupted and more problematic to define. Therefore data were examined with respect to time after Stage 1 onset (there were no cases of WASO between initial stage 1 onset and stage 2 onset).

EEG was visually scored by two raters such that 4 of the 7 extended nights were scored by both raters. The inter-rater reliability was calculated by comparing agreements and disagreements epoch by epoch, and was 89.0%.

For display and calculations, SWA is expressed as a percent of the mean of all 20 second epochs of NREM stages 2, 3, and 4 for the first 8 hours of the extended sleep period (similar to Dijk et al, 1991). In addition to the full Delta (0.75-4.5 Hz) band, the $Delta_{Low}$ (0.75-2.5 Hz) was also used in calculation. $Delta_{Low}$ was used so that the SWA criteria may more closely reflect the criteria used in visual sleep scoring (Rechtschaffen and Kales, 1968), and that low theta activity would not contaminate the SWA measure. However, there was almost no difference between these two bands, so only $Delta_{Low}$ was used in graphics.

Sleep Data

Total minutes spent in each sleep stage were compared for the first 7 hours of the extended night and the first 7 hours of the previous night. T-tests were done between total minutes spent in each stage of sleep on both nights, and showed no significant differences. So the initial part of the sleep period did not differ from the previous normal night, meaning there was likely no significant disturbance from adaptation occurring.

To first examine the data at a descriptive level, Figure 1 shows the CBT, sleep stage scoring, and SWA data ($Delta_{Low}$ in NREM) for each subject. As expected, each subject showed high amounts of SWS and SWA at the beginning of the night, that then decreased toward minimum levels near hours 8 and 9, when a normal sleep period would likely terminate. Similarly, REM periods increased in length toward hours 8 and 9. A correspondence can be seen between high levels of SWA and stages 3 and 4. Subjects showed an increase in waking toward the end of the sleep period, but this usually involved bouncing between stages Wake, 1 and 2, such that subjects were not completely awake for long periods (subjects 2 and 3 showed the longest sustained waking periods, while subject 7 had almost no waking).

It is evident that during the final 5 hours of the sleep period, several subjects (most notably 2, 5, 6, and 7) reached levels of SWA exceeding 200% of the average for the first 8 hours. SWA levels were not as high as at the beginning of the night, but they clearly had not dropped to an asymptote. SWS also occurred during this period, approximately synchronized with the SWA increases.

The average time course of waking, REMS, SWS, and SWA in NREM sleep for 1 hour and 3 hour blocks are shown in Figures 2 and 3 respectively. It is evident from Figure 1

Figure 1(a): CBT, sleep stage,
and SWA (power) data for Subject 1 in Study 1

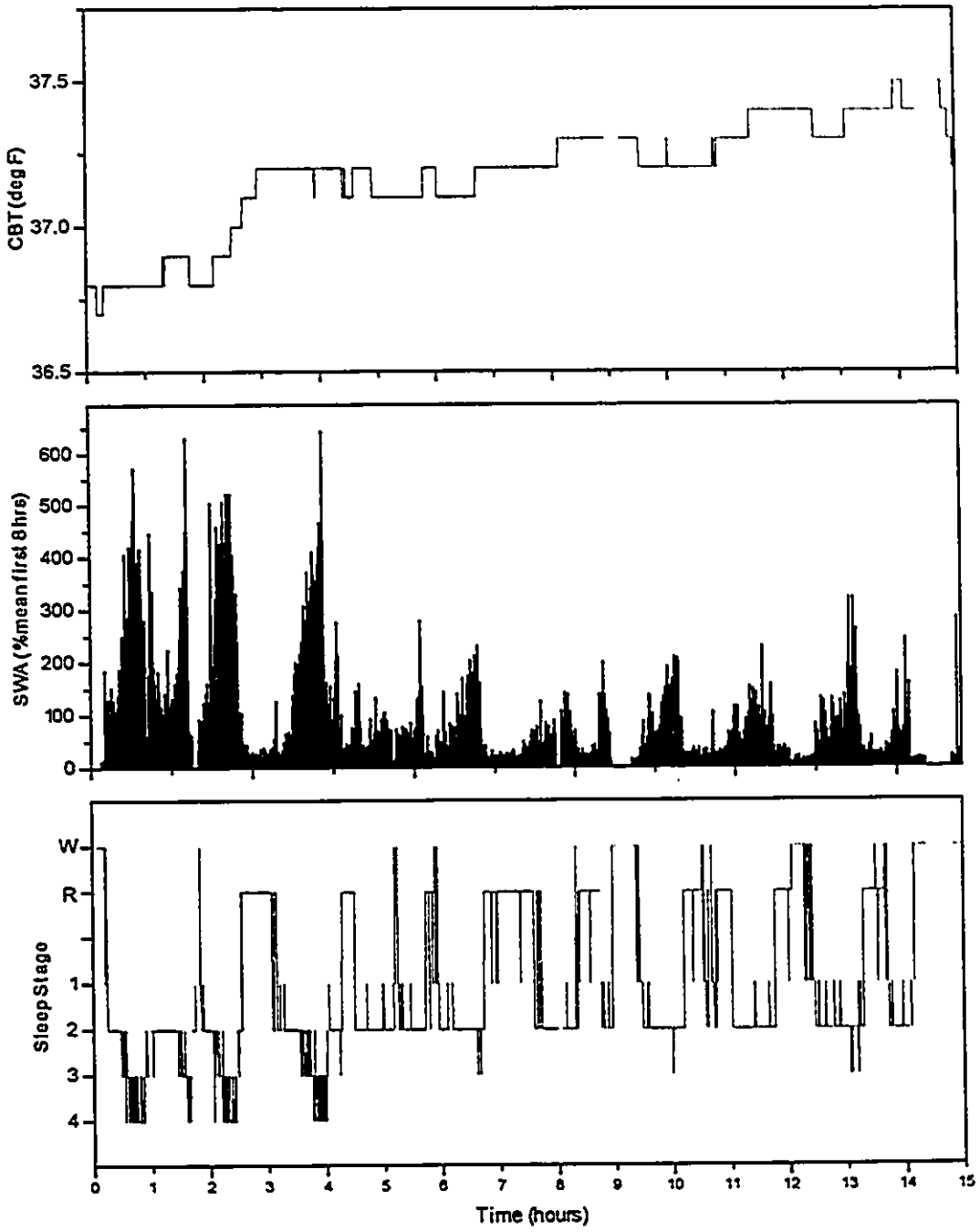


Figure 1(b): CBT, sleep stage,
and SWA (power) data for Subject 2 in Study 1

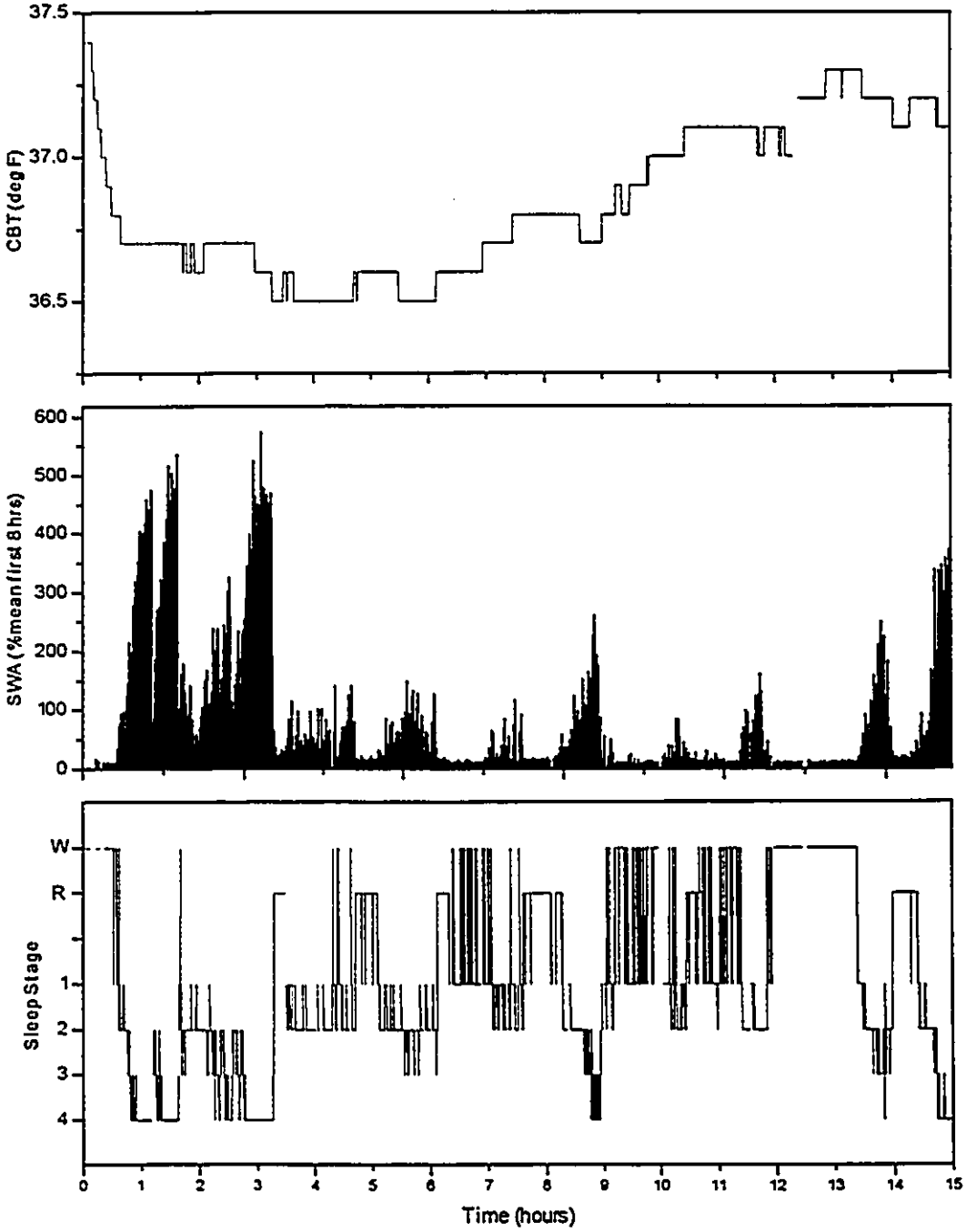


Figure 1(c): CBT, sleep stage,
and SWA (power) data for Subject 3 in Study 1

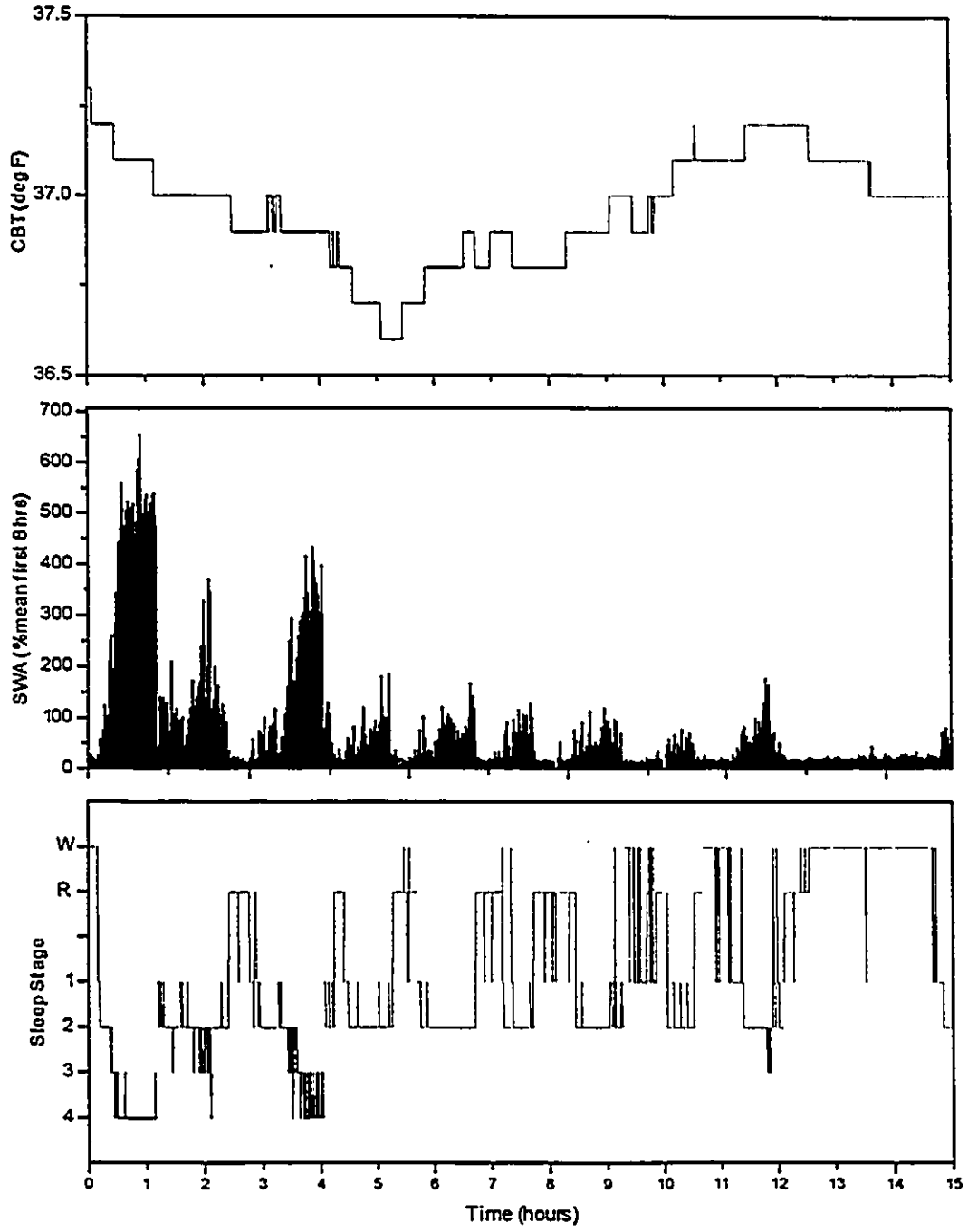


Figure 1(d): CBT, sleep stage,
and SWA (power) data for Subject 4 in Study 1

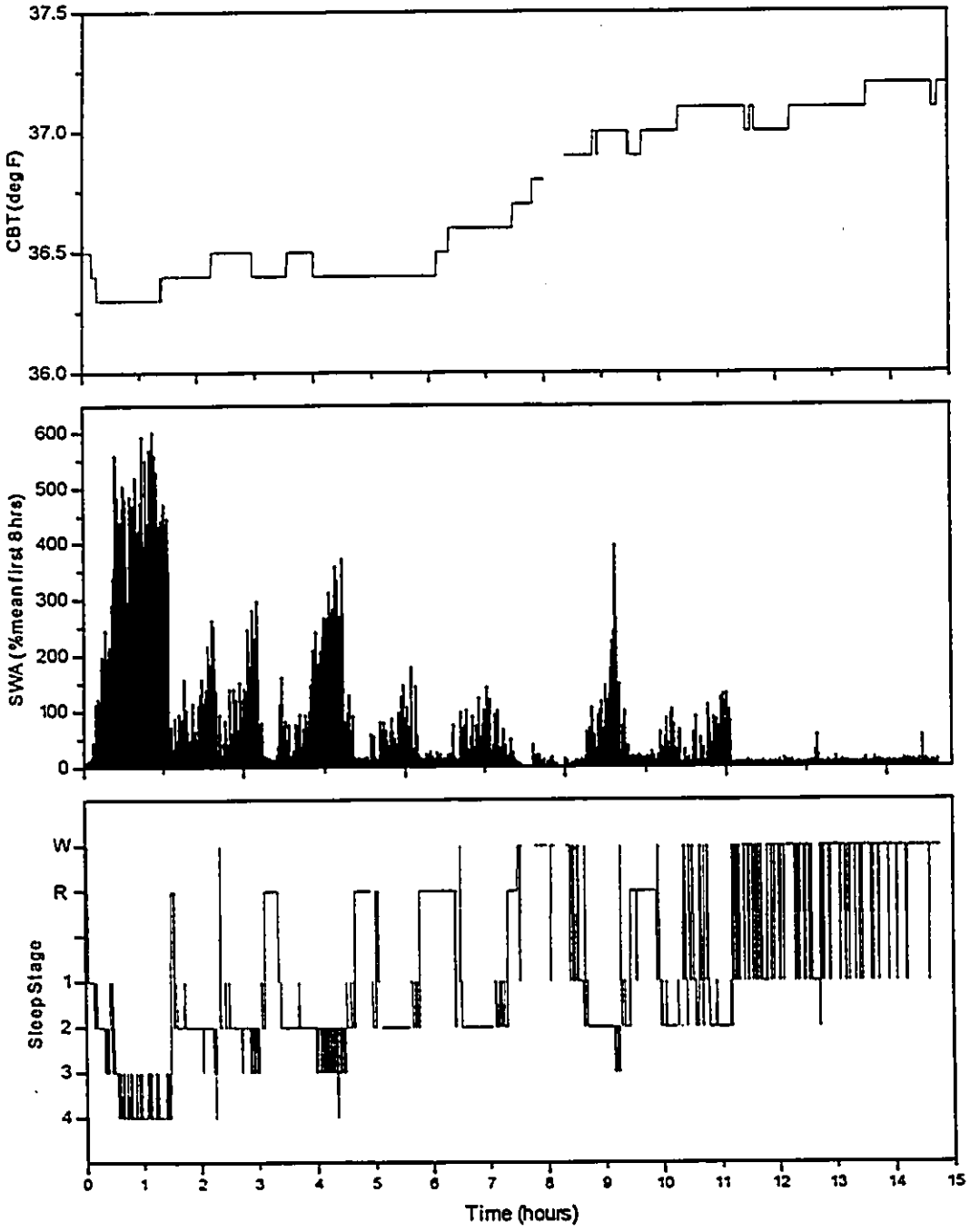


Figure 1(e): CBT, sleep stage,
and SWA (power) data for Subject 5 in Study 1

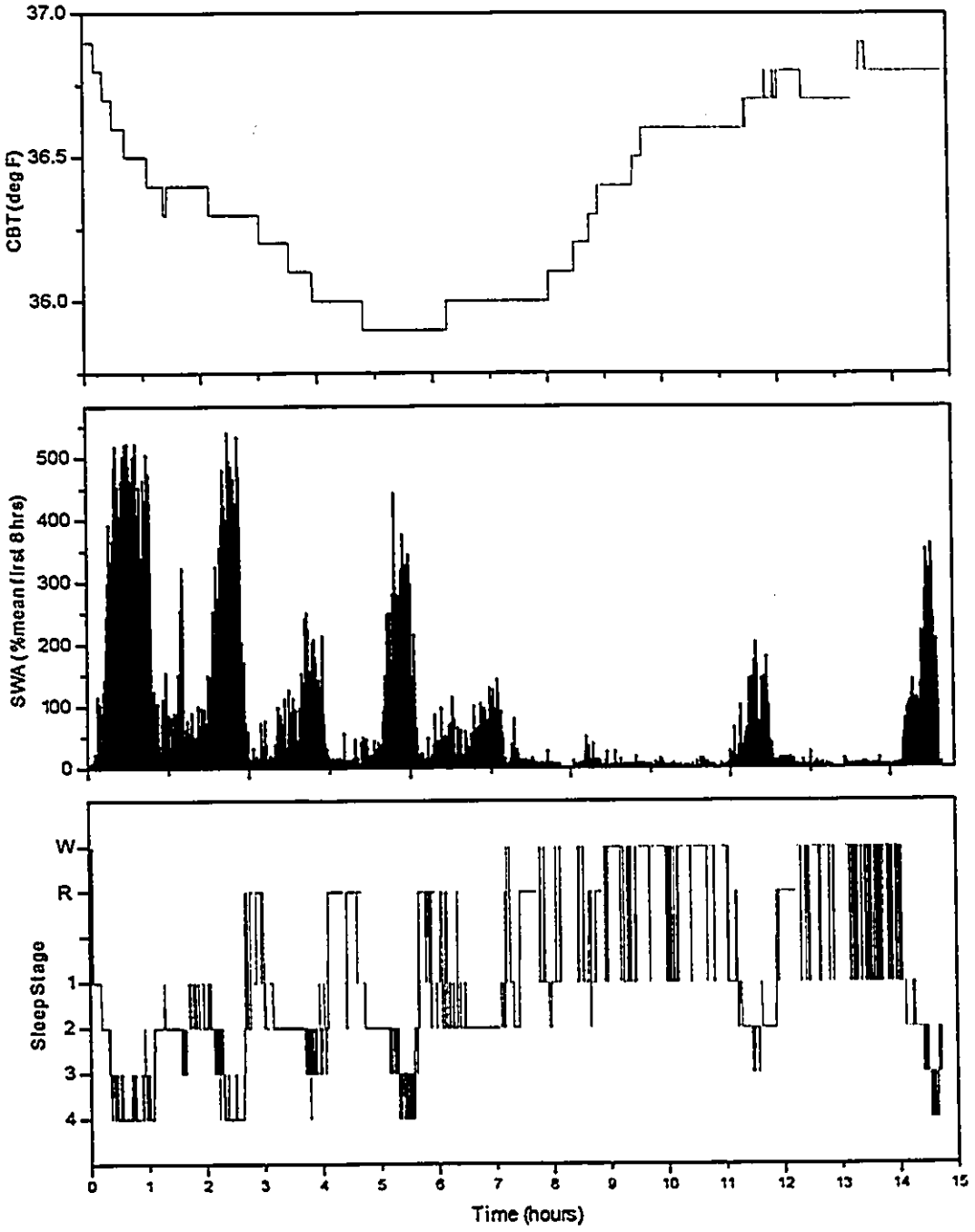


Figure 1(f): CBT, sleep stage,
and SWA (power) data for Subject 6 in Study 1

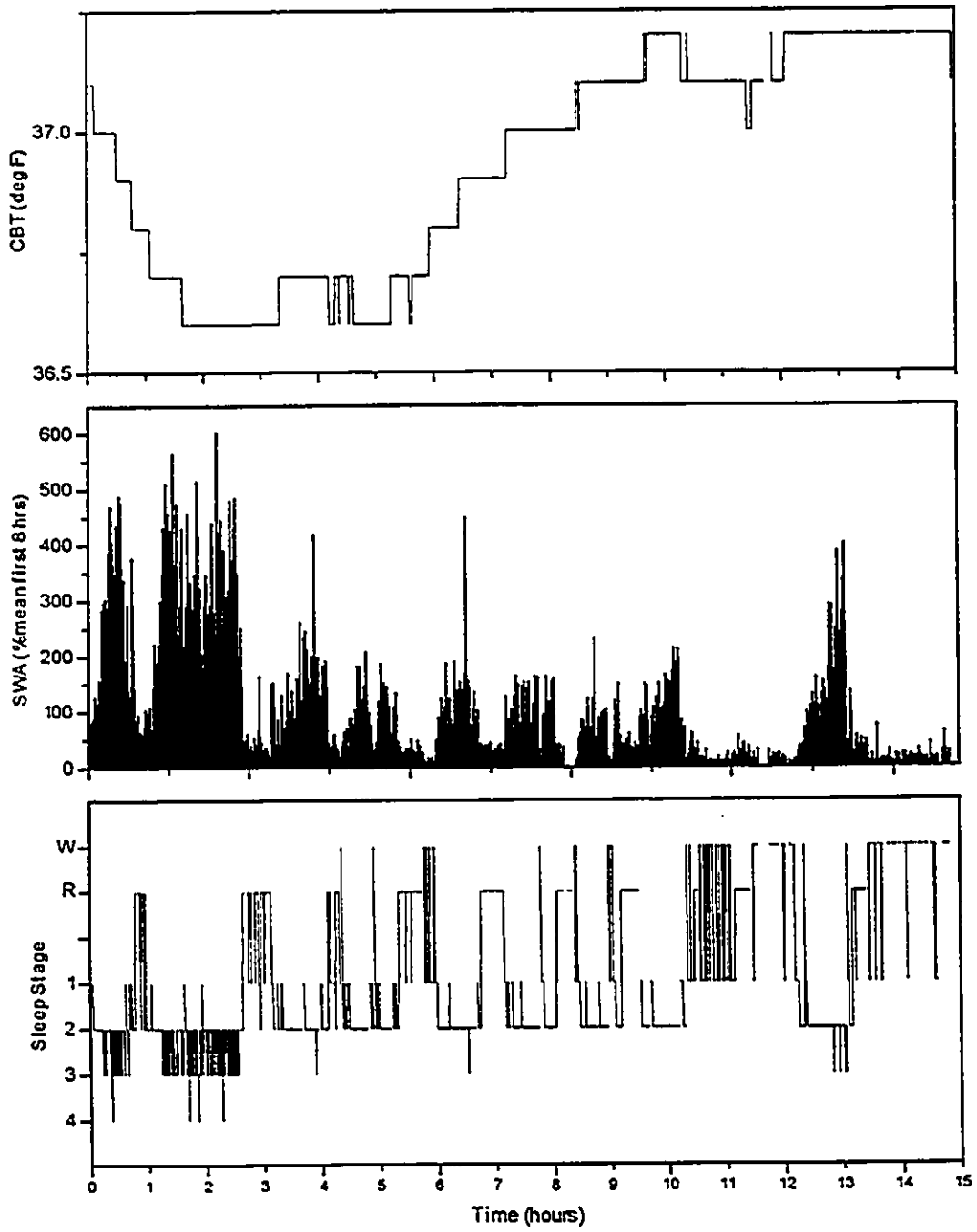


Figure 1(g): CBT, sleep stage,
and SWA (power) data for Subject 7 in Study 1

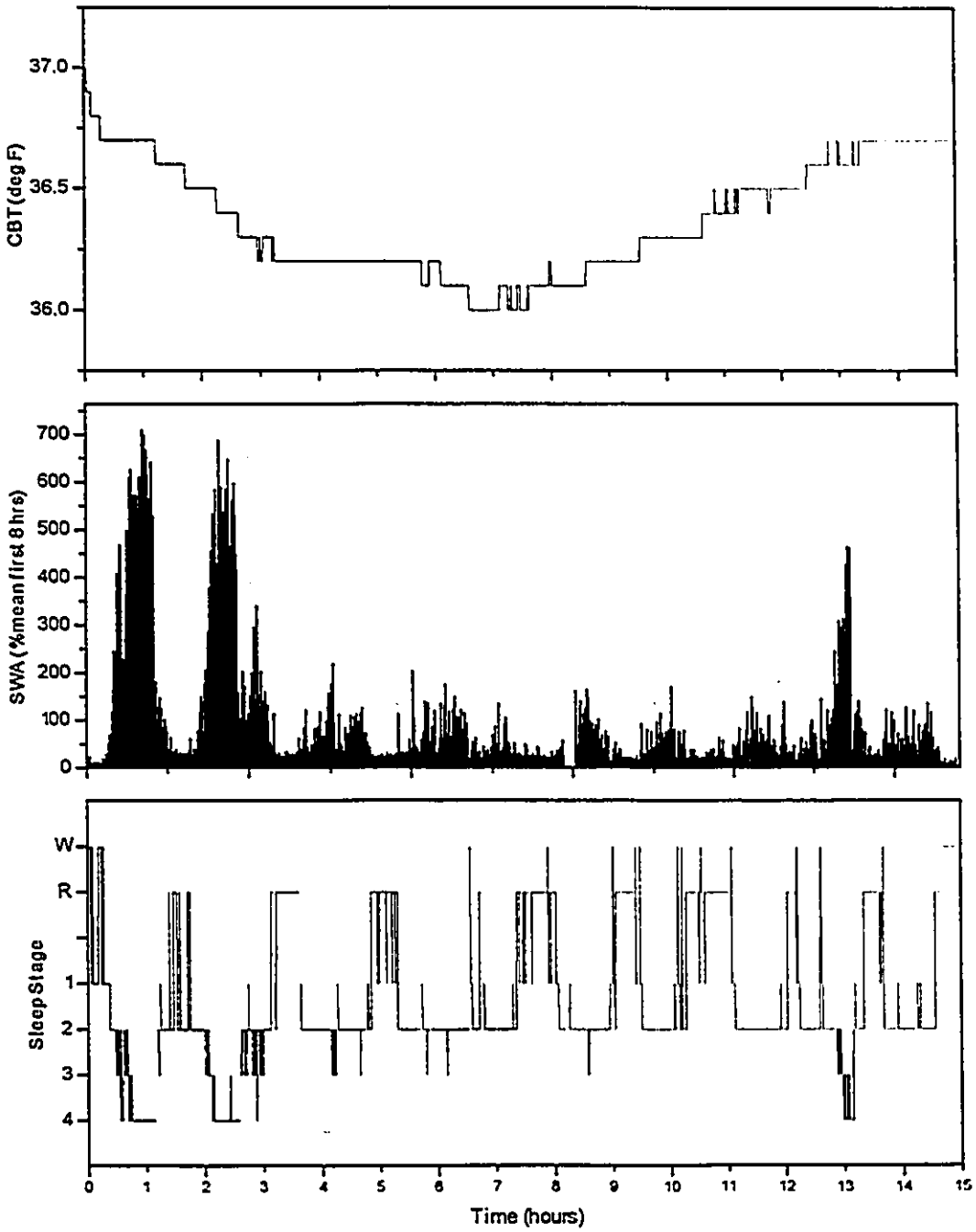


Figure 2: Average time course for Wake, REM, SWS, and SWA in NREM for 1-hour blocks

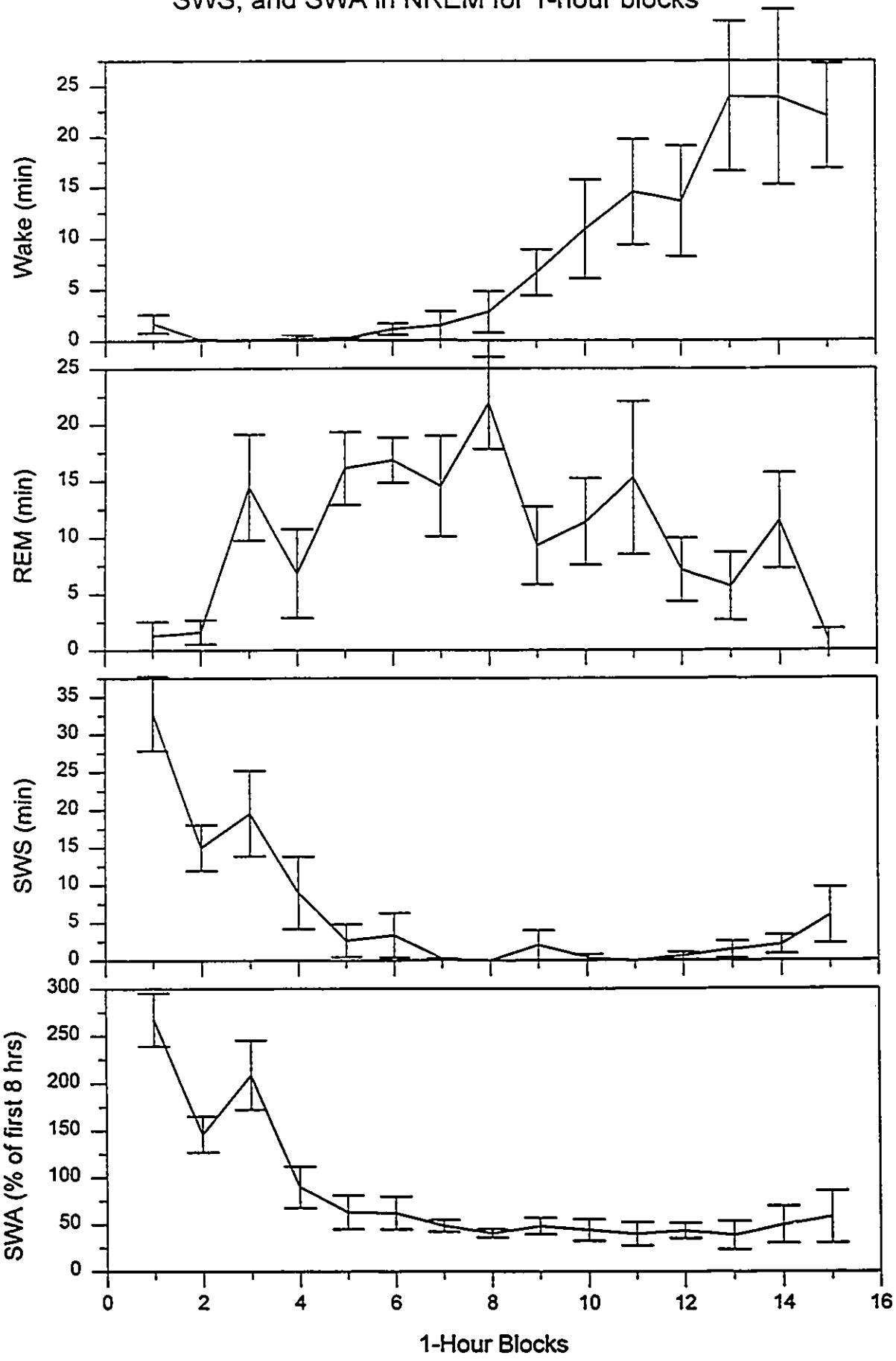
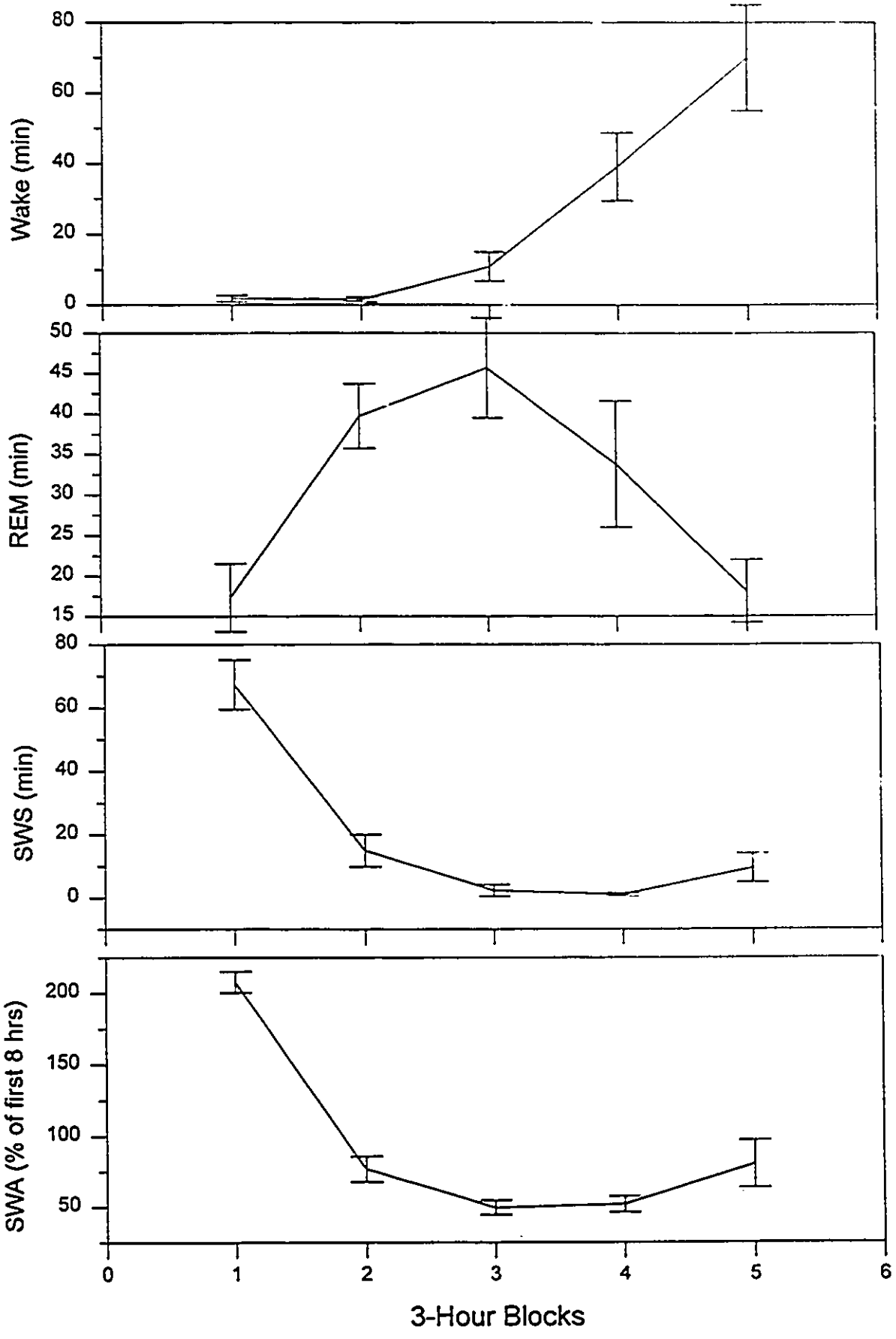


Figure 3: Average time course for Wake, REM, SWS, and SWA in NREM for 3-hour blocks



that there was much variation between subjects at any one time, therefore averaging across subjects may obscure data, especially concerning small SWS and SWA rebounds that may occur at different times in each subject. However, some trends emerge from these averaged data. It can be seen from Figures 2 and 3 that the expected rapid early decline in SWS and SWA occurred, but also that there was a late rise in SWS and SWA that was more pronounced with the 1 hour blocks (Figure 2). Wake time increased with time asleep, but showed a small decrease at hour 12, followed by a steep rise, then decreased in the 14th and 15th hours. REM sleep followed an inverted U shape with its maximum being in the 8th hour. It also showed a jagged pattern, reflecting how the REM periods of the NREM-REM cycle crossed the hourly units. REM and SWS or SWA seemed to mirror each other to some degree.

Proceeding to statistical analysis of these data, sleep stage and SWA data are shown as means and percentages of TST (with standard error) for 3 hour blocks in Table 1. Repeated measures ANOVAs were used to analyze changes in each variable. If effects were significant, adjacent intervals were then compared using matched pair t-tests. Significance levels were corrected for multiple comparisons using the Bonferonni adjustment.

Most of the significant differences were found between the 0-3hr block and the 4-6hr block, as the SWS and SWA measures (Stage 3, Stage 4, SWS, Delta, $Delta_{Low}$) decreased from their high early levels, and Stage 2 and REM sleep increased to occupy a larger proportion of sleep. There was a significant rise in Waking during the 10-12hr block. There was also a significant drop in Stage 1 during the 13-15hr block, accompanied by a drop in Total Sleep Time (TST). This drop in TST without a concurrent increase in Waking is partially accounted for by an increase in epochs rejected for movement artifact. Although there was an increase in all

Table 1
Sleep stages in minutes and percent of total sleep time (with SEM), and ANOVAs, for 3-hour blocks of the extended sleep period.

	3-Hour Block						
Stage	0-3	3-6	6-9	10-12	12-15	F	p<
W	1.8 (0.9)	1.5 (0.7)	10.9 (4.1)	39.1 (9.6)*	69.9 (15.0)	14.89	.0001
1	11.5 (2.5)	16.3 (3.8)	25.2 (7.4)	34.0 (5.8)	18.6 (3.4)*	4.46	.008
2	77.3 (6.5)	101.0 (4.0)*	80.4 (10.8)	59.5 (9.1)	41.8 (12.2)	9.79	.0001
3	24.2 (3.0)	11.0 (3.4)*	1.5 (1.1)	1.0 (0.5)	4.6 (1.6)	16.44	.0001
4	43.1 (9.3)	4.0 (2.1)**	0.8 (0.8)	0.0 (0.0)	4.9 (3.0)		note[1]
SWS	67.3 (7.8)	15.0 (5.1)**	2.3 (1.9)	1.0 (0.5)	9.5 (4.6)	39.33	.0001
REM	17.3 (4.2)	39.7 (4.0)*	45.7 (6.2)	33.8 (7.8)	18.1 (3.9)	6.06	.002
TST	173.4 (1.1)	172.0 (1.5)	153.6 (7.2)	128.3 (11.7)	88.0(16.1)*	16.45	.0001
1%	6.6 (1.4)	9.5 (2.3)	17.1 (5.2)	29.6 (6.3)**	31.1 (11.8)	3.44	.023
2%	44.5 (3.6)	58.8 (2.4)*	51.7 (5.5)	45.1 (3.3)	40.6 (8.6)	NS	NS
3%	14.0 (1.7)	6.3 (2.0)*	1.0 (0.7)	0.9 (0.4)	4.8 (1.6)	12.73	.0001
4%	24.9 (5.4)	2.3 (1.2)**	0.5 (0.5)	0.0 (0.0)	4.2 (2.5)		note[1]
SWS%	38.9 (4.5)	8.6 (2.9)**	1.5 (1.2)	0.9 (0.4)	8.9 (3.8)	32.51	.0001
REM%	10.0 (2.5)	23.0 (2.2)*	29.7 (3.6)	24.5 (3.9)	19.4 (4.4)	4.80	.005
SWA in NREM							
0.75-4.5Hz	203.7 (6.8)	77.0 (8.4)***	53.1 (5.3)	55.9 (5.5)	83.3 (16.4)	43.71	.0001
0.75-2.5Hz	207.7 (7.4)	76.6 (9.1)***	49.4 (5.1)	51.8 (5.6)	80.2 (16.8)	43.99	.0001

*p<.05, **p<.01, ***p<.001
note[1] = There was not enough variance in the 10-12 hour block to allow an ANOVA, so the simple t-tests were done between adjacent groups.

SWS and SWA for the 13-15hr block over the 10-12hr block, it was not significant. These analyses were done for comparison with Dijk et al. (1991), and results are similar. However, to look for a small late SWS or SWA return it seems logical to test not adjacent intervals, but rather to compare the postulated central minimum to the late return. Therefore, a t-test was used to compare the final block (13-15hr) to the middle block (7-9hr) for SWS and SWA. Since an increase in SWS and SWA had been predicted, and observed, 1-tailed tests of significance were used. With this test, SWS showed a significant increase ($t=-2.45$, $df=6$, $p<.025$), as did SWA ($t=-2.08$, $df=6$, $p<.05$).

In addition, the trend analyses for SWS and SWA were of interest. The time course of SWS showed significant quadratic ($F(1,6)=34.76$, $p<.002$) and cubic ($F(1,6)=8.29$, $p<.028$) trends. SWA also showed significant quadratic ($F(1,6)=51.39$, $p<.001$) and cubic ($F(1,6)=16.99$, $p<.006$) trends. The significant cubic trend was unexpected from the shape of the distribution, but when the amount of variance explained by each trend was calculated, the quadratics contributed 42% for SWS, and 50.5% for SWA, while the cubics accounted for only 3% and 3.5% respectively. So both quadratic and cubic trends were statistically significant, but the cubic trend's contribution was relatively unimportant next to the large contribution of the quadratic. As has been pointed out before (Dijk et al., 1991), a significant quadratic component does not necessarily indicate a late increase in data, and may reflect merely a curved descent. So the significant quadratic trends for SWS and SWA do not prove a late return. This issue will be dealt with later using curve fitting.

To address the issue of the magnitude of SWA in the late part of the sleep period, 3 hour means may be an inappropriate measure for the shorter SWS/SWA periods late

Table 2

Maximum 5 minute SWA mean in each 3-hour block during 15 hours of sleep

Block	1-3Hr	4-6Hr	7-9Hr	10-12Hr	13-15Hr
5MinMax(mean)	452.2	211.4**	100.3*	108.5	194.0

*p<.05 **p<.01 (t-test)

in extended sleep. Shorter periods would be expected of the minor pole of a 12 hour rhythm. Accordingly, we selected the maximum 5 minute average within each 3 hour period to give another indication of the magnitude of SWA reached over short SWS episodes at the various times of sleep. Table 2 shows the maximum 5 minute average for SWA ($Delta_{Low}$) in the 3 hour blocks across the sleep period.

A one-way repeated measures ANOVA showed a significant effect [$F(4,24)=14.65$, $p<.001$, with quadratic trend significant, and cubic trend not significant]. As occurred previously, the main differences with t-tests between adjacent groups appear to be with the large SWA decline in the early part of the sleep period. However, if the final block (13-15Hr) was compared to the middle block (7-9Hr), then there was a significant difference ($t=-2.11$, $df=6$, $p<.05$, 1-tailed). So the SWS and SWA data appeared to follow an approximately U-shaped function (or reverse J), and differences between the center low and late increase are significant.

Relationship of Late SWS and SWA to WASO, REM, and WASO+REM

To investigate the possibility that SWS or SWA in the extended portion of the sleep period were related to prior waking or REM sleep, correlations were performed between the

mean SWS or SWA in the last 3 hours of sleep, and prior WASO, REM, and WASO + REM. Spearman correlations were used because a linear relationship between variables was not postulated. The analysis for SWS and SWA were treated separately. The overall alpha level for each set of 3 correlations (WASO, REM, and WASO+REM) was $p<.05$, so that the significance criterion for each comparison was $p<.017$. From the literature review, the predicted relationships would be positive between late SWS or SWA and WASO, REM, and WASO+REM, so 1-tailed tests of significance were used. The WASO and REM amounts were calculated for the period from sleep onset to the maximum 15 minutes of SWA in the last 5 hours of sleep (Max_{Late}, to be defined in detail below).

None of the correlations between late SWS or SWA and WASO, REM, or WASO+REM was significant, even before correction for multiple comparisons ($df=5$, $p<.05$). Correlations of SWS or SWA to WASO were in the positive direction, but those with REM were close to zero. Thus the late return of SWS and SWA appeared to be independent of WASO and REM.

To summarize, the course of SWS and SWA can be seen to decrease across the sleep period, there is an increase in SWS/SWA over preceding intervals after 12 hours, and this increase is not related to WASO or REM. However, averages for SWS and SWA in the last 3 hours of sleep are a very crude measure for a return of SWS or SWA, and may reflect a persistence rather than a return. It appeared then that a more specific definition for a return of SWS/SWA was needed in order to estimate not only if there was a return, but also the time when it occurred and an estimate of how much it increased over previous levels. Such a definition is presented below.

Definition of a SWA Return and Its Timing

A "return" implies that the SWS or SWA must have

disappeared or diminished prior to the late part of the extended sleep, so the late sleep must be examined with reference to prior sleep. SWA was the measure chosen to calculate this return because it is the more objective measure, and because it yields a continuous variable, which makes differentiation of smaller adjacent blocks easier than with the interval scale of stage scoring (SWS).

Five minute means of SWA were combined into 15 minute running averages (i.e., each 5 minute period was included in 3 consecutive 15 minute averages). The maximum 15 minute average in the last 5 hours of sleep became a candidate for a SWA return. If the value of this 15 minute average was greater than all such 15 minute averages for the previous 4 hours, it was considered to be a return of SWA. The criterion of exceeding the previous 4 hours was chosen because that includes approximately 2 NREM-REM cycles with less SWA, implying a return. Although the NREM-REM cycle is likely to be disrupted by this point in extended sleep, this seemed a logical time-frame to use. The center of this maximum 15 minute interval was considered to be the time of that SWA return.

Fifteen minute averages were chosen because the SWS and SWA episodes late in the sleep period are often short, and 15 minutes gives an average that does not include much, if any, sleep of other stages. This helped to determine the magnitude of solely the SWA. The criterion used for the magnitude of the SWA return was the value for the maximum 15 minute SWA running average in the last 5 hours of sleep (Max_{Late}), with the maximum 15 minute running average during the preceding 4 hours (Max_{Prev4}) subtracted. This gives the amount the SWA has increased over what it had already been during the last 2 sleep cycles. This value was then expressed as a percentage of the Max_{Prev4}, using the formula:

$$Return_{Mag} = (Max_{Late} - Max_{Prev4}) / Max_{Prev4} * 100$$

where:
$Return_{Mag}$ = the magnitude of the SWA return as a percent of the maximum in the previous 4 hours;
Max_{Late} = the maximum 15 minute running average in the last 5 hours;
Max_{Prev4} = the maximum 15 minute running average in the 4 hours preceding Max_{Late}.

Thus a positive number means a SWA return, and a negative number indicates no SWA return but instead a decrease. The size of the number indicates how much of an increase has occurred relative to the maximum level in the previous 4 hours (two sleep cycles). For example, if $Return_{Mag}$=100%, then a SWA return that is double the size of the maximum in the previous 4 hours has occurred.

The presence or absence of SWA returns, and their timing, along with CBT phase, to be described later, are shown in Table 3. Figure 4 shows these data. According to the above definition, 5 of the 7 subjects have SWA returns ranging from 41.6% to 402.1%. One subject shows a slight decline of SWA (-8.3%), while another shows a larger decline (-62.3%). So the majority of subjects appear to have had a resurgence of SWA in sometimes large amounts after at least 4 hours of lower levels. A matched pair t-test between the values of Max_{Late} and Max_{Prev4} for all subjects, including the 2 with no SWA return, approached significance ($t=1.818$, $df=6$, $p<.07$, 1-tailed. A directional test was used due to the previously cited evidence to predict a SWA increase; see Ferguson, 1981). Therefore, there appears to be a return of SWA during the final 5 hours in 5 of the 7 subjects, but over all subjects the increase in SWA over levels in the previous 4 hours did not amount to a statistically significant difference. For all subjects with this SWA return, it occurred beyond 12.5 hours (average 13.8 hours).

Figure 4: SWA return magnitude and CBT phase (as delay from sleep onset to CBT minimum)

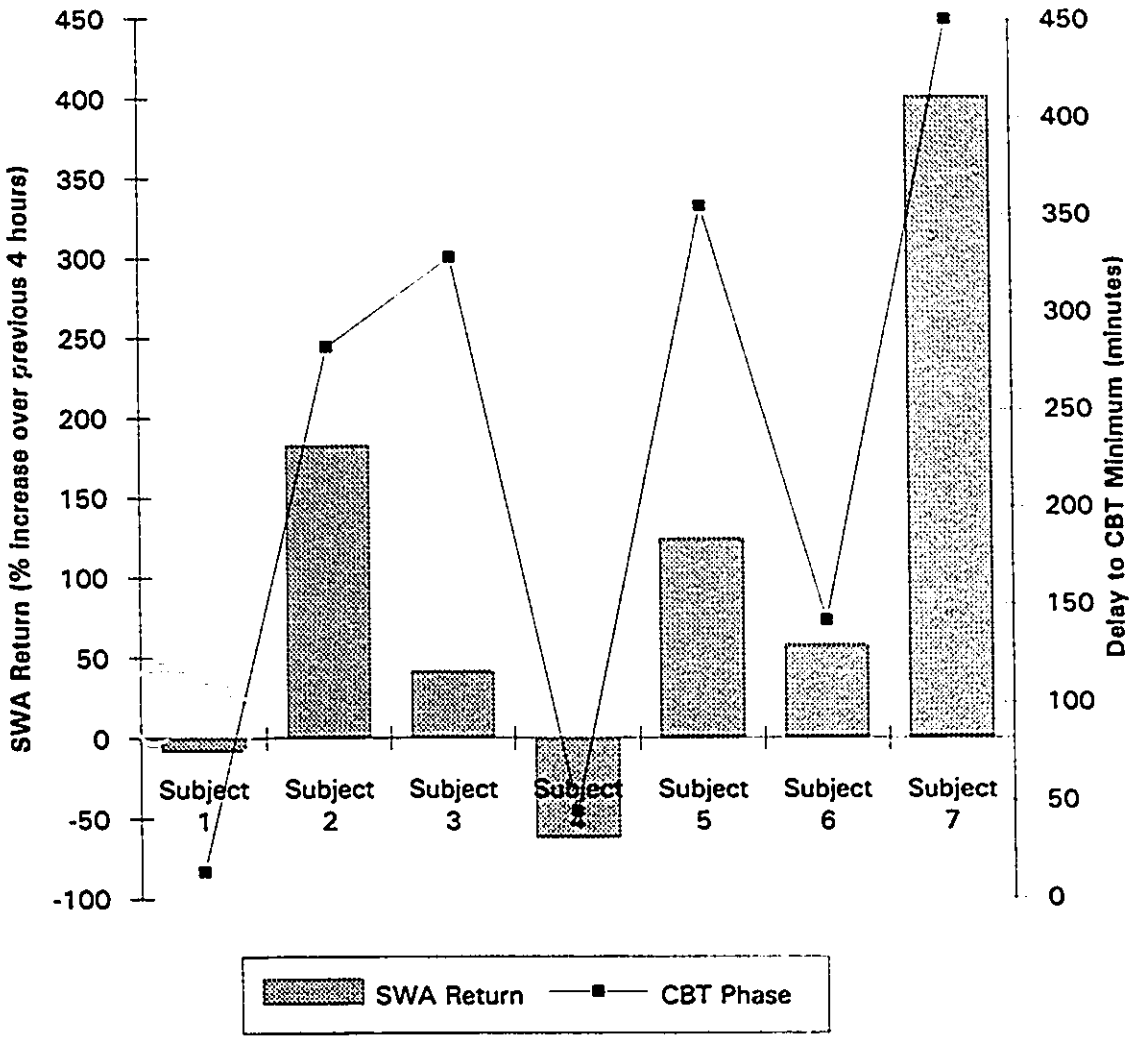


Table 3

Maximum 15 minute SWA means in the last 5 hours of extended sleep (Max_{Late}), maximum 15 minute SWA mean within 4 hours prior to Max_{Late} (Max_{Prev4}), magnitude of the SWA return, time of SWA return, and CBT phase and amplitude for Study 1.

	Measure					
Subj	Max_{Late}	Max_{Prev4}	$Return_{Mag}$	Time	CBT Phase	CBTAmp
1	99.53	108.50	-8.26	12.75	0.23	1.60
2	322.71	114.16	182.68	14.33	4.70	3.60
3	105.53	74.51	41.64	14.83	5.47	2.97
4	54.26	144.23	-62.38	10.92	0.75	2.33
5	209.30	93.27	124.41	14.42	5.90	4.24
6	183.73	116.27	58.01	12.80	2.37	2.33
7	268.00	53.38	402.06	12.83	7.50	3.60

Max_{Late} and Max_{Prev4} are in arbitrary units.
$Return_{Mag}$ = $(Max_{Late}-Max_{Prev4})/Max_{Prev4}*100$
Time = time from sleep onset to Max_{Late} in hours
CBT Phase = time from sleep onset to CBT minimum in hours
CBT Amp = CBT drop + rise during sleep in degree Fahrenheit

Curve Fitting to Mean SWS and SWA Data

Curve fitting is another way that has been used to examine the issue of late SWS or SWA increases in extended sleep. Is the course of SWS or SWA best described by an exponentially decreasing function, or by a U-shaped function with a return of SWS or SWA after 12 hours?

Three curves were fit to 60 minute averages and 30 minute averages of SWS and SWA. These intervals were chosen to give a reasonable number of data points for fitting a curve, while also smoothing the raw data to some extent. One curve exponentially decreased over time (Curve 1), another one was a second degree polynomial with only a linear and quadratic component (Curve 2), and a third one used an exponential decrease but allowed a linear increase to be added 12 hours after sleep onset (Curve 3).

An exponentially decreasing function for SWS and SWA is what the Two Process Model predicts (Process S), and the equation used here was similar to that of Kecklund and Akerstedt (1992):

$$SWS \text{ or } SWA = P1 + P2^{-P3*Time} \qquad \text{(Curve 1)}$$

where:
Time = the time in hours since sleep onset;
P1 = SWA as Time approaches infinity, so P1 should approach 0;
P2 = the y intercept (when Time = 0), when added to P1;
P3 = coefficient of the exponential function.

Parameters were estimated using non-linear regression in the statistics program Systat.

The fit of Curve 1 was compared to the fit given by a simple second order polynomial:

$$SWS \text{ or } SWA = P1 + P2*Time + P3*Time^2 \qquad \text{(Curve 2)}$$

where:
Time = the time in hours since sleep onset;
P1 = the y intercept (when Time = 0);
P2 = the linear coefficient;
P3 = the quadratic coefficient.

A second degree polynomial was chosen because theoretically the two components should account for much of the variance, the linear capturing much of the decrease in SWS and SWA over time, and the quadratic accounting for the curvature of the descent and allowing for an increase of SWS or SWA late in the sleep period. Certainly a higher order polynomial would fit the data more closely, but there would be no theoretical basis for each added component, making their interpretation difficult. As was mentioned earlier, a significant quadratic component does not necessarily indicate a late increase in the data, and may reflect a curved descent. By fitting Curves 1 and 2, we can compare which one explains more variance, and especially which one fits the data better in the extended part of the night.

To further check if a late increase component improves

fit over a simple exponential decrease, Curve 1 was modified to include a late increase after the initial exponential decline:

$$SWS \text{ or } SWA = P1 + P2^{-P3 \cdot Time} + P4 * (Time_{12}) \qquad \text{(Curve 3)}$$

where:
P1, P2 and P3 are the same as in Curve 1;
$Time_{12}$ = time in hours starting at 12 hours after sleep onset;
P4 = coefficient for a linear increase to begin 12 hours after sleep onset.

The P4 term adds an increase to the exponential decline starting 12 hours after sleep onset. If this explains more variance than Curve 1, it would support the notion of a late return of SWS or SWA. A linear component was chosen for its simplicity to capture a late rise, and not to imply that a linear increase would continue beyond 15 hours. Again, this was averaged data, with subjects individually showing short late SWS and SWA episodes of various magnitudes at various times.

Table 4

Amount of Variance Explained by Curves 1, 2, and 3 for 60 Minute and 30 Minute Means of SWS and SWA

Curve	SWS		SWA	
	60Min	30Min	60Min	30Min
Curve 1	90.2	69.8	88.0	73.3
Curve 2	89.0	71.1	85.8	74.2
Curve 3	92.8	71.7	88.8	74.1

Figure 5 and 6 show the 3 different curves fitted to SWS and SWA data respectively (both 60 minute and 30 minute averages). Curve 1 postulates no return of SWS or SWA late in the night, while Curves 2 and 3 can rise near the end of the sleep period. The variance explained by each curve is shown in Table 4. The curves all fit the 60 minute data better than the 30 minute data, due to the greater smoothing of hourly averages. For the hourly data, all three curves explain a large part of the data (over 89%), with the two exponential curves giving a better fit. Of the two exponential curves, Curve 3 explained more variance than Curve 1 (2.6% more for SWS; 0.8% more for SWA). With the 30 minute data, the polynomial Curve 2 gave a better fit than Curve 1. By allowing for a late rise in SWS or SWA, Curve 3 explained more variance than Curve 1 in all cases, however, it must be noted that differences were relatively small (60 Min: 2.6% for SWS, 0.8% for SWA; 30 Min: 1.9% for SWS, 0.8% for SWA). It should also be noted that Curves 1 and 3 are not identical up to the 12 hour point, because parameters were estimated with an additional component in Curve 3. However, when the parameter estimates of Curve 1 (P1, P2, and P3) are substituted into Curve 3, the two functions become identical up to 12 hours, and only one parameter is estimated (P4). When this substitution was made, Curve 3 still gave a better fit than Curve 1 (60Min: Curve 3 is 1.7% better for SWS, 0.5% for SWA; 30Min: 1.2% for SWS, 0.4% for SWA), but the fit was not as good as when all parameters were estimated together in Curve 3. These differences after substitution of parameter estimates are due solely to the simple linear increase of Curve 3 after 12 hours. This indicates that a simple exponential decrease in SWS and SWA over time asleep explains much of the observed data, but that allowing an increase after 12 hours (giving a reverse J shaped function) explains slightly more variance. So a

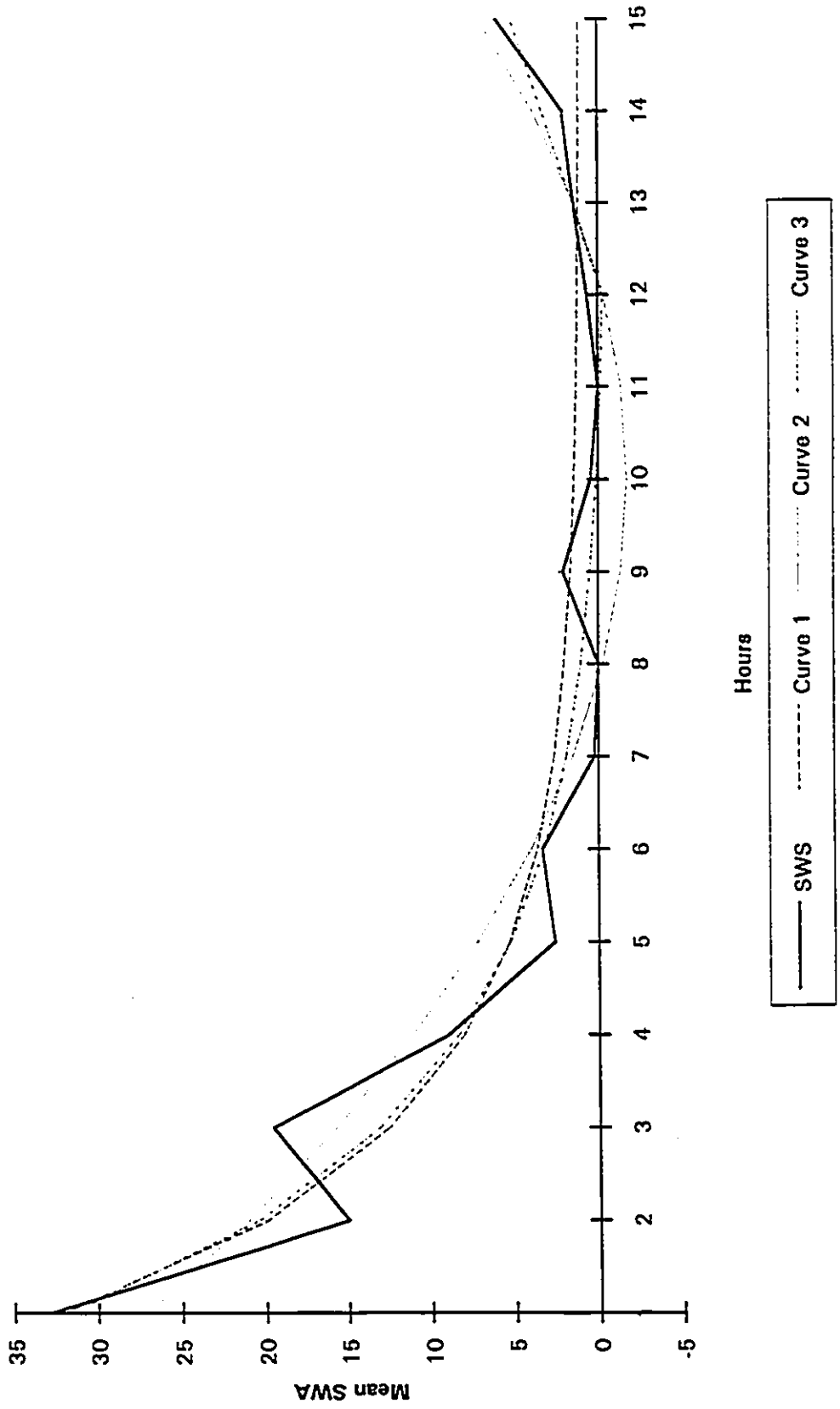


Figure 5(a): Curves fitted to SWS data in 60-minute blocks

Figure 5(b): Curves fitted to SWS data in 30-minute blocks

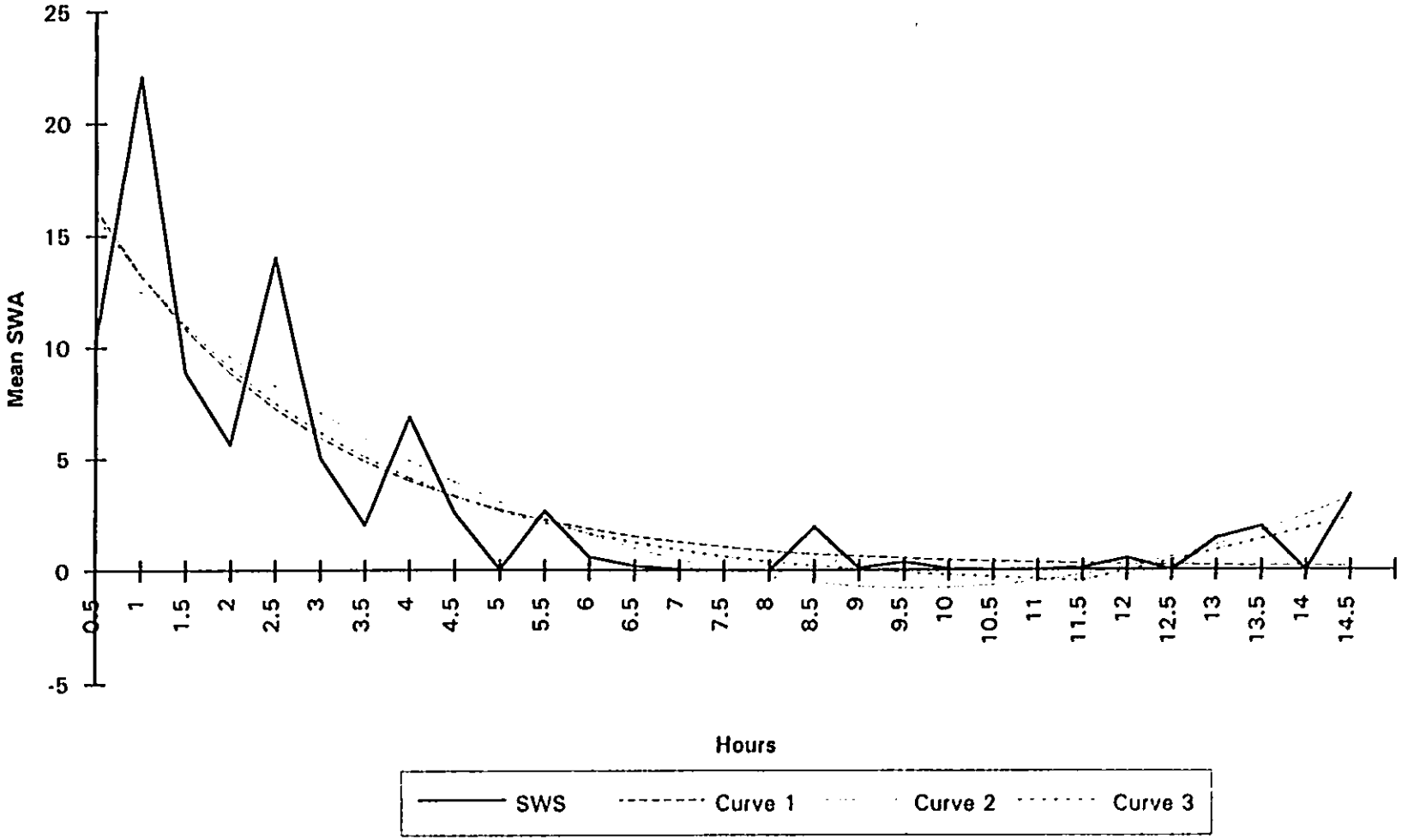
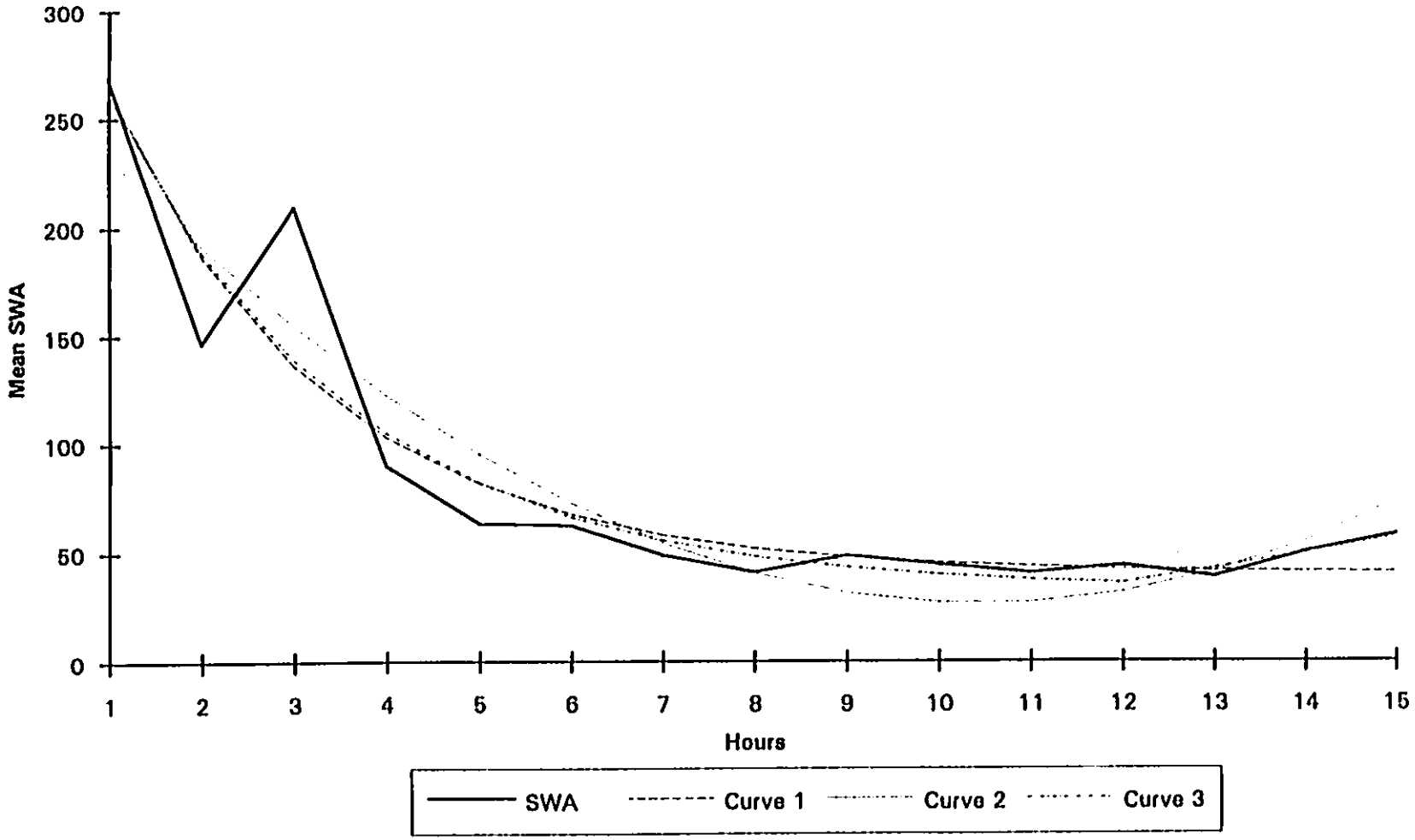


Figure 6(a): Curves fitted to SWA data in 60-minute blocks



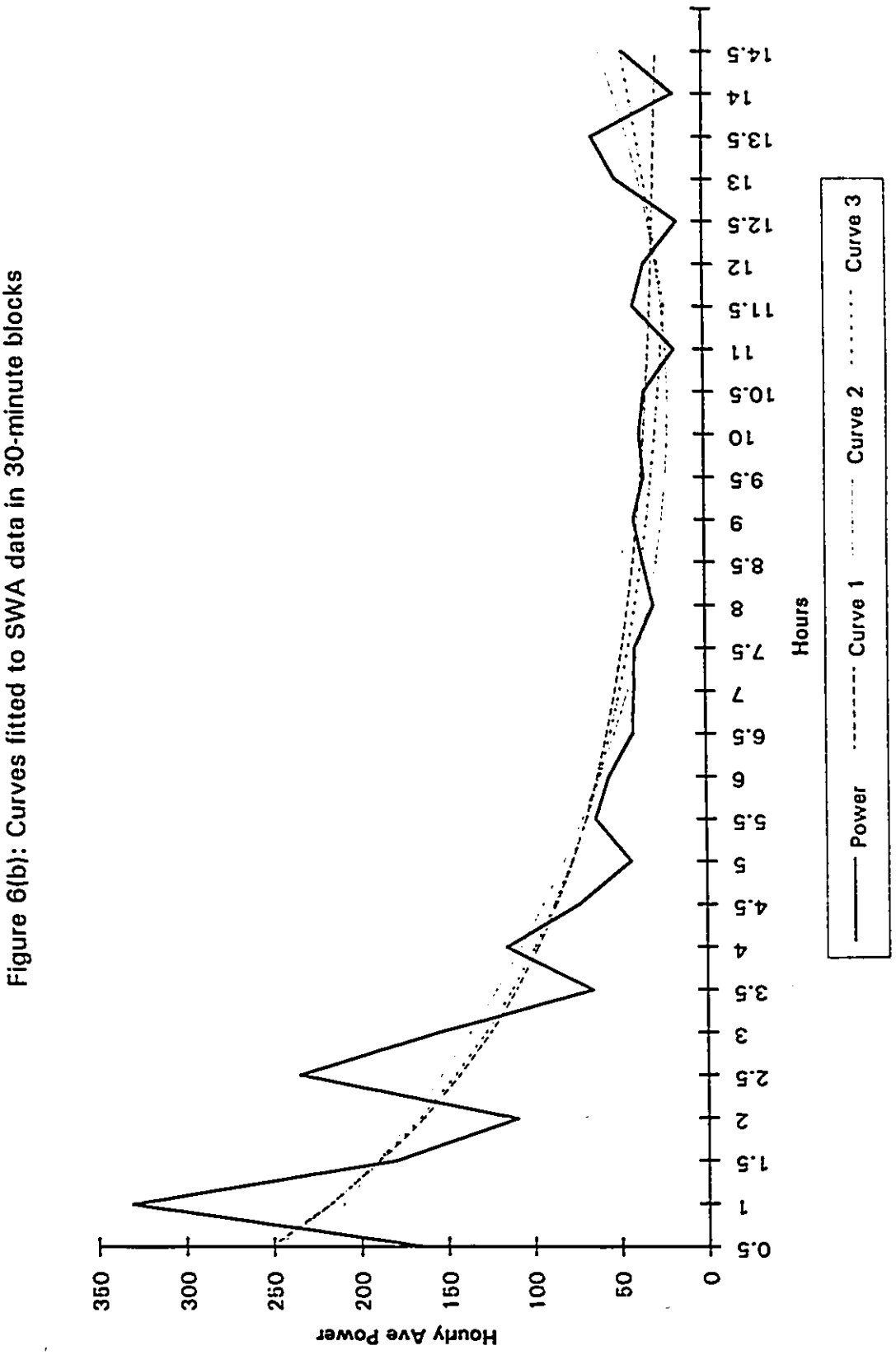


Figure 6(b): Curves fitted to SWA data in 30-minute blocks

significant quadratic trend more likely reflected a return, and not just a curved descent of SWS and SWA.

CBT Data

The CBT data from Figure 1 show that there was variation between subjects, but in general there was a decline of CBT after sleep onset, then a rise toward the end of the sleep period. Several subjects reached a maximum that again began to drop before the end of the data collection period. In two subjects the minimum was at or very near sleep onset (CBT phase advanced relative to other subjects), and these subjects also showed the lowest SWS and SWA in the extended portion of sleep. In order to compare CBT characteristics to those of SWS and SWA, some measures for CBT must be defined.

CBT Phase

The circadian rhythm of CBT was under investigation for a possible link to the postulated 12-hour rhythm of SWS and SWA, so CBT phase had to be determined. Ideally, some form of constant routine would be used to establish CBT phase, but that was not possible for this study, both methodologically and due to resources. So the CBT minimum during the 15 hour sleep period was used as the marker for CBT phase. This measure of CBT phase made sense also in that if there is a thermoregulatory aspect to SWS and SWA, then the actual CBT during the sleep period should mean more than a measure some time before or after that sleep period.

Several methods are possible for estimating the time of CBT minimum. It is possible to simply take the center of the set of minimum values in the raw data, or smoothed data. However, when data fluctuate around the minimum, one reliable point may be difficult to determine. Another method that has been used is to fit a cosine curve with a period of 24 hours to the data. Working here with only 15 hours of data, this turned out to give a generally bad fit, with the

minimum zone of the raw data being clearly far from the cosine minimum in many cases. The method selected was to fit a 9th degree polynomial curve to the raw CBT data. This essentially smooths the data in a very reliable way, that is sensitive to local fluctuations, and yields a single minimum point close to the minimum in the raw data. It provided an easily replicable, objective estimate for a single minimum point. Only one case posed a problem, when the minimum was very close to sleep onset (Subject 1), so in this case the point was chosen at the midpoint of the raw data minimum, which was clear in this data set (see Figure 1). The fitted CBT curves are shown in Appendix 2, and delay from sleep onset to CBT minimum (CBT phase) is shown in Table 3.

CBT Amplitude

Amplitude of CBT change (CBT amplitude$_{ch}$)was defined as the absolute value of the drop in CBT from sleep onset to CBT minimum, plus the rise from CBT minimum to the eventual maximum. This was done because simply giving the range of CBT values would miss that over the same range, some subjects started at low CBT before dropping then rising to a higher CBT, changing over the range once, while others started at high CBT and dropped greatly then rose again to that high CBT, essentially covering the range twice. CBT amplitude$_{ch}$ is shown in Table 3 (in degrees Fahrenheit).

CBT phase and the CBT amplitude$_{ch}$ were correlated to determine if the two measures were related, and there was a significant relationship (r_s=.873, df=5, p<.02, 1-tailed). This was not surprising, since if there were a long delay to CBT minimum, then CBT would likely drop and rise to the daily maximum, while if there were a short delay to minimum, CBT would drop slightly then rise to that same maximum. So it was reasonable to expect that if one of these CBT factors were associated with late SWS or SWA, that the other may also have been related. Because of this strong relationship,

only CBT phase was examined statistically, in order to keep power higher with the relatively small sample size (n=7), and because CBT phase was more related to timing issues that were to be investigated in Study 2.

Relationship of CBT to Late SWS and SWA

For these calculations, SWS, SWA, magnitude of the SWA return, and timing of SWA return were treated separately. Tests of significance were 1-tailed since positive correlations were predicted.

SWS in the last 3 hours showed a significant correlation to CBT phase (r_s=.714, df=5, p<.05). The correlation between SWA in the last 3 hours and CBT phase was non-significant (r_s=.357, df=5, p>.05). This indicates that CBT phase was significantly related to at least late SWS in extended sleep.

When CBT phase was correlated to the magnitude of the SWA return ($Return_{Mag}$ in Table 3), there was a significant relationship (r_s=.786, df=5, p<.04), which can also be seen in Figure 4. So CBT phase was associated with late SWA increases over levels in the previous 4 hours. The timing of these late SWA episodes was investigated for relationships to CBT phase, and proved to be positive but non-significant (r_s=.649, df=5, p>.05).

Cross Correlation of CBT to SWA

To investigate the possibility that SWA is involved in thermodownregulation, cross correlation analysis was done between the CBT and the slope of the CBT curve with SWA ($Delta_{Low}$) using 5 minute means. The analysis was done up to lag 60 (measuring 2.5 hours each direction).

The cross correlation of CBT to SWA showed 2 different patterns: subjects 1,3,4, and 5 and showed no relationship, whereas subjects 2, 6, and 7 showed significant positive correlations (p<.05) of SWA to CBT between 70 to 135 minutes earlier (lag -14 to -27), and negative correlations to CBT

about 175 minutes later (lag 34 to 36). These 3 subjects showed a relationship between the time course of SWA and CBT such that there was a small positive relationship between the two curves (i.e., similarly shaped distributions), with points on the SWA curve relating to points on the CBT curve somewhat earlier. Since the CBT curve is approximately a U-shaped curve for these subjects, this analysis would be consistent with both curves having an approximately U-shaped distribution, with the CBT curve advanced slightly relative to the SWA curve. This would mean that CBT changes were occurring before SWA changes. To determine if these calculations actually reflected a SWA return or simply the initial decline in SWA and CBT near sleep onset, similar cross correlations were performed on created data, between a U-shaped curve and a curve decreasing to an asymptote, or an identical decreasing curve that had a late rise to approximately 50% of the starting value (as was observed in the SWA of these subjects, in a reverse J shape). These tests showed that cross correlations of a U-shaped curve to a decreasing curve showed a similar shape, but that only cross correlations to the curve with a late return showed significant ($p<.05$) relationships. These relationships were stronger at slightly negative time lags. This suggests that at least in some subjects, there is a small relationship between the time course of SWA and CBT, although this may reflect similarly shaped rhythms, rather than one influencing the other.

All of the subjects with this CBT to SWA relationship were previously mentioned as having the most prominent SWS and SWA returns (except for subject 5, who had a SWS/SWA episode approximately 5.5 hours into the sleep period, very near the CBT minimum, the likely cause of the difference from the other SWS/SWA return subjects).

Cross correlation revealed no consistent relationship

between rate of change in CBT (slope) and SWA. This is not surprising since it has already been noted that SWA is high during the rapid drop of CBT at the beginning of sleep, and is also present in smaller amounts during the rising CBT late in the sleep period. Similar cross correlations between SWA and CBT, or CBT slope, for only the last 3 hours were done to investigate if the late SWA pulse was associated with any CBT changes; no association was found. These cross correlation analyses would be very important measures if SWA is supposed to play a role in CBT regulation. Despite the finding that there is a relationship between the shape of the SWA and CBT distributions in some subjects who showed late SWA increases, the lack of a relationship between CBT or slope of CBT curve and SWA seems to indicate that SWA does not play a significant role in CBT regulation.

It is possible that there is some threshold level of SWA above which there would be a relationship of SWA to CBT change. No such relationship was found. There were high levels of SWA during many different levels of CBT, and at different CBT slopes, so it appears that SWA may have a course in some cases similar to that of CBT, but that CBT was independent of the immediate level of SWA (i.e., SWA does not seem to cause CBT decreases).

Study 2

Hypotheses

Hypotheses (1) and (2) were the same as in Study 1:

1) There should be a 12-hour rhythm of SWS/SWA pressure, such that SWS/SWA should return 12.5 hours after sleep onset in extended sleep. Since this should be a biological rhythm, the amount of SWS/SWA in the return should be independent of the amount of intervening WASO, REM, and WASO+REM.

2) There should be a relationship between CBT and SWS/SWA.

3) Bright light should be able to reset CBT phase independent of timing of sleep.

Predictions

1) There should be a return of EEG slow wave activity (detected by visual scoring, and spectral analysis) approximately 12.5 hours after the first appearance of SWS. This return of SWS/SWA should be unrelated to intervening WASO and/or REM sleep amounts.

2) Morning bright light should phase advance the CBT rhythm, and evening bright light should phase delay the CBT rhythm.

3) The phase advance in CBT rhythm should be accompanied by an advance in the return of EEG SWA, and a phase delay in CBT rhythm should be accompanied by a delay in the return of EEG SWA.

Method

Subjects

Subjects were selected for their ability to extend their sleep, as indicated by a sleep habits questionnaire. Subjects spending large amounts of time outdoors in sunlight (e.g. outdoor employment) were excluded. Eleven subjects were selected for the next step, which was a preliminary long sleep during which subjects were monitored by an Actillume (accelerometer) while sleeping at home. Of these 11 subjects, 8 who showed long sleep with few interruptions, were subsequently interviewed to screen for any medical or psychological problems and completed an MMPI. The final selection criterion was a baseline 15 hour sleep in the lab (8HBL, to be explained later), which caused us to reject 5 subjects who could not extend their sleep past 9 hours. Three male subjects (age 19, 21, and 29) were selected for the experiment. None took drugs or medication, and were instructed not to nap or consume alcohol or caffeine during the testing periods. They were also requested to refrain from any extensive exercise during the testing periods. Subjects were compensated $500.00 for their participation.

Design

Subjects slept in the laboratory for 4 series of 4 nights each. The overall design is shown in Table 5. There were 4 series of nights so that there were 2 for baseline measures, and 2 during which CBT was manipulated by bright light. One baseline series was to give extended sleep data for more normal circumstances, with 8 hours of sleep during each night of the series and 15 hours of sleep on the final night (8HBL). The other baseline (6HBL) involved 6.5 hours of sleep each night prior to the extended night, to give baseline measures for the 2 bright light conditions which required shorter durations. Bedtime was at 23:00h for all nights of all conditions.

Each subject slept alone in a windowless, sound attenuated room during sleep recording. The first night served for adaptation as well as screening for sleep disorders. The second two nights of 6.5 hours provided baseline measures, and also standardized the amount of prior waking before the subsequent extended night; this may have caused sleep restriction for long sleepers, but was necessary to apply bright lights close to the minimum of CBT to cause a larger CBT rhythm shift without changing sleep timing. Upon awakening, subjects were kept in the laboratory from 6:00h-9:00h (during 8HBL, it was 7:30h-9:00h), while they watched television. Subjects also came to the laboratory in the evening to again watch television for 3 hours (20:00h-23:00h). During these 3 hour periods, subjects were monitored to prevent falling asleep. During the 8HBL and 6HBL, the television periods were conducted in regular room light (<250 lux). There was one series with morning bright light (ML), when banks of lights on both sides of the television delivered bright light (7000-11000 lux) to the subject during the morning period (6:00h-9:00h), but the evening period (20:00h-23:00h) was in room light (<250 lux).

TABLE 5

Design for Study 2

SERIES 1: 8 Hour Baseline (8HBL)

	Day 1	Day 2	Day 3	Day 4
MORNING		<250 Lux (6-9 am)	<250 Lux (6-9 am)	<250 Lux (6-9 am)
EVENING	<250 Lux (20-23pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)
Sleep:	Adaptation (8 hrs)	Baseline (8 hrs)	Baseline (8 hrs)	Extended (15 hrs)

SERIES 2: 6.5 Hour Baseline (6HBL)

	Day 1	Day 2	Day 3	Day 4
MORNING		<250 Lux (6-9 am)	<250 Lux (6-9 am)	<250 Lux (6-9 am)
EVENING	<250 Lux (20-23pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)
Sleep:	Adaptation (6.5 hrs)	Baseline (6.5 hrs)	Baseline (6.5 hrs)	Extended (15 hrs)

SERIES 3: Morning Light (ML)

	Day 1	Day 2	Day 3	Day 4
MORNING		7000-11000 Lux (6-9 am)	7000-11000 Lux (6-9 am)	7000-11000 Lux (6-9 am)
EVENING	<250 Lux (20-23pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)	<250 Lux (20-23 pm)
Sleep:	Adaptation (6.5 hrs)	Baseline (6.5 hrs)	Baseline (6.5 hrs)	Extended (15 hrs)

SERIES 4: Evening Light (EL)

	Day 1	Day 2	Day 3	Day 4
MORNING		<250 Lux (6-9 am)	<250 Lux (6-9 am)	<250 Lux (6-9 am)
EVENING	7-11000 Lux (20-23pm)	7000-11000 Lux (20-23 pm)	7000-11000 Lux (20-23 pm)	7000-11000 Lux (20-23 pm)
Sleep:	Adaptation (6.5 hrs)	Baseline (6.5 hrs)	Baseline (6.5 hrs)	Extended (15 hrs)

[Bedtime 23:30h on all nights]

The opposite was done during an evening light (EL) series, when room light (<250 lux) was present during the morning period (6:00h-9:00h), and bright light (7000-11000 lux) was present during the evening period (20:00h-23:00h). The ML and EL conditions were presented after the 2 baselines. Each series was separated by at least 2 weeks to let phase shifts re-adjust to normal conditions.

The light exposure was done to phase advance (ML), or phase delay (EL) subjects' CBT curves relative to the sleep/wake cycle. CBT was measured continuously for each series of 4 days, and also for the day preceding the series with bright light exposure (5 days).

Regarding safety of the bright lights, no dangerous side effects have been documented in the literature for exposure to light of the intensity and duration used in this experiment (e.g., see Avery, 1992).

To control for amount of light exposure outside the lab, each subject wore an Actillume (Cole et al., 1992; Kripke and Cole, unpublished), which continuously measured their light exposure, 24 hours a day, during each 4 day testing period. Subjects were also instructed to avoid being outdoors as much as possible, to reduce the amount of bright light received outside the laboratory. The same Actillume unit contained an accelerometer measuring movement to detect any napping during the same period. The Actillume also stored the CBT data from a rectal temperature sensor.

Measures

Standard polysomnographic measures were recorded continuously every night using the same equipment and procedures described for Study 1. CBT was recorded using a disposable rectal probe (YSI 4491A) and sampled at a rate of every 60 seconds, 24 hours a day, being recorded on the external channel of an Actillume.

The bright light was delivered using an array of lights

(2 "Sunbox" units), set at an intensity of 7000-11000 lux, measured at eye level. The light arrays emit full spectrum light, without ultraviolet light.

Light was administered by having subjects watch a television placed directly between the two light arrays from a chair at a standard distance from the screen, such that the subject's eyes were approximately 65 cm from the light sources and television screen. At this distance, light intensity was approximately 7000-11000 lux, measured at eye level. This configuration was chosen because horizontal gaze at the television screen would consistently deliver more light to the eye than if subjects were looking down to read on the table surface (Dawson and Campbell, 1990). A "twilight" period of 3000-6000 lux light was used during the first 15 minutes at the beginning of morning light, and the last 15 minutes at the end of evening light. Subjects in the room light condition were exposed to light of less than 250 lux for the same 3 hour periods.

EEG, EMG, and EOG signals were computer analyzed and visually scored using the same equipment and procedures as in Study 1. EEG was visually scored by two raters such that 75% of the extended nights were scored by both raters. The inter-rater reliability was 88.7%.

To further track subjects' daily activities, they filled out daily event logs of what happened away from the laboratory.

Results

Due to the small sample size (n=3), statistical analysis is limited, so data will be discussed more at a descriptive level.

The results of the MMPI screening are in Appendix 1, along with those for Study 1, and showed that subjects were within normal ranges.

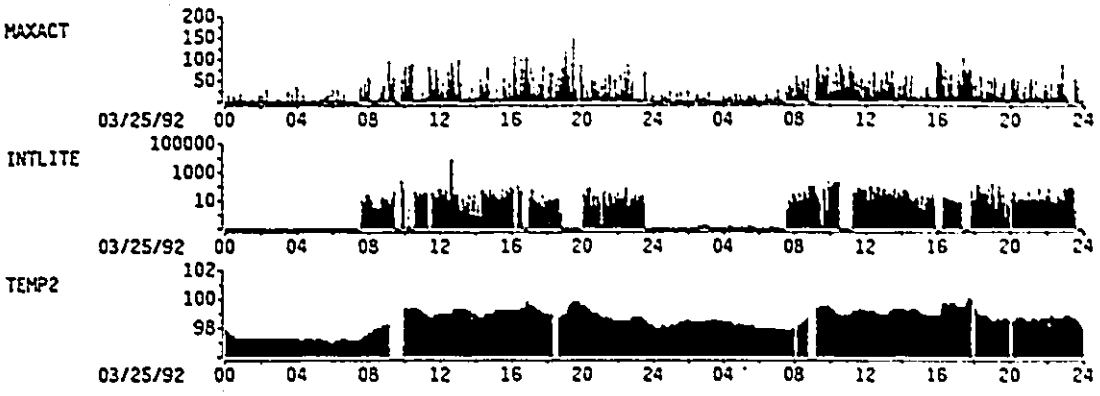
Actillume Data

The CBT, activity,and light exposure data collected by the Actillume is included in Appendix 3, and will be discussed in this section. The Actillume data clearly show the experimental manipulations. Figure 7 shows an example of a day from each series. Figure 7(a) and 7(b) show the 8HBL and 6HBL. The light levels only occasionally exceed 1000 lux, and this is typically near the middle of the day, when there should be little phase shifting effect on CBT. There are brief periods without light, when the Actillume was covered by a jacket while outside, however, subjects spent very little time outside (never exceeding 25 minutes at a time). Figure 7(c) shows the ML condition, with high levels of light between 6:00h and 9:00h. Figure 7(d) shows EL, with the bright light between 20:00h and 23:00h.

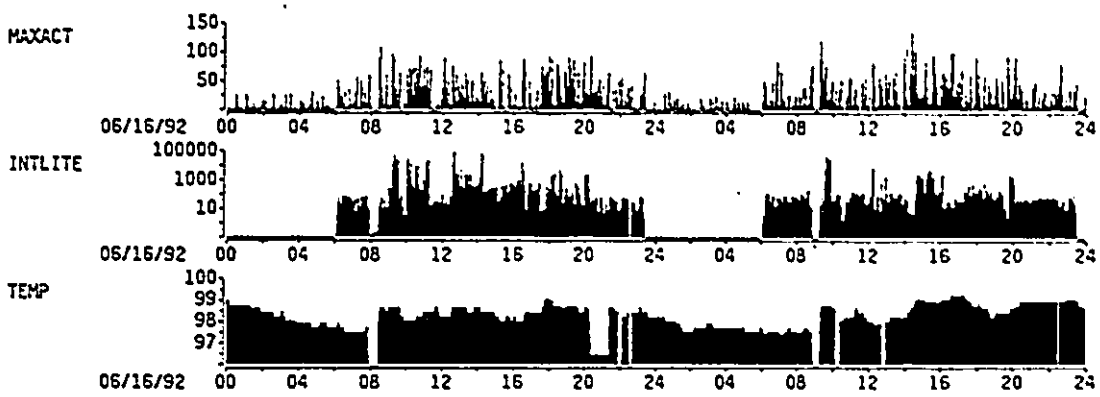
Because the light sensor on the Actillumes was covered for short periods of time (e.g., by coats to protect from rain or cold) in a non-systematic way, the mean light received over each series was not considered to be a reliable measure of light exposure, and is accordingly not reported. In any case, the light data (Appendix 3) show that during the bright light periods, 6:00-9:00h for ML and 20:00-23:00h for EL, the subjects were exposed to bright light (in the order of 10,000 lux), and low light levels (less than 250 lux) were observed during the dim light period of ML (20:00-23:00h), and EL (6:00-9:00h), and during both of these periods for the 8HBL and 6HBL conditions. Also, no sustained exposure (i.e., hours) to bright light outside the laboratory was detected on the Actillume record. Thus the experimental manipulation appeared to have been delivered successfully, and subjects were free from uncontrolled bright light outside the laboratory.

Figure 7
Examples of Actillume data from each condition of Study 2

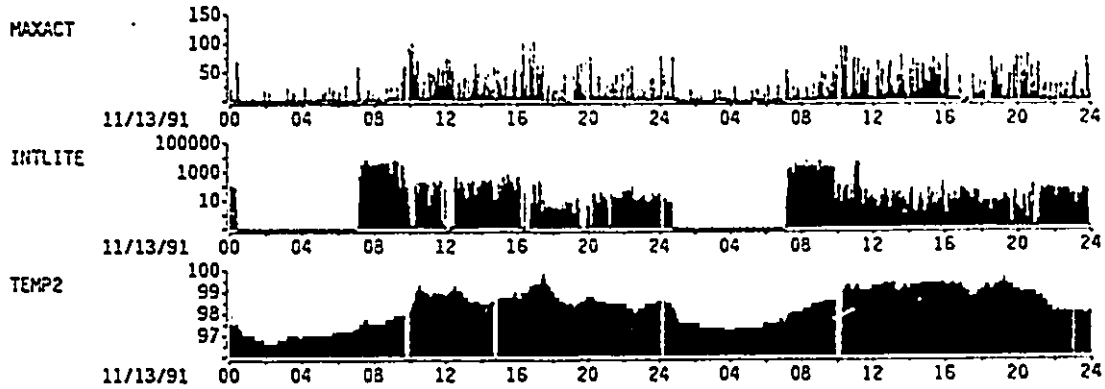
(a) 8 Hour Baseline



(b) 6.5 Hour Baseline



(c) Morning Light



(d) Evening Light

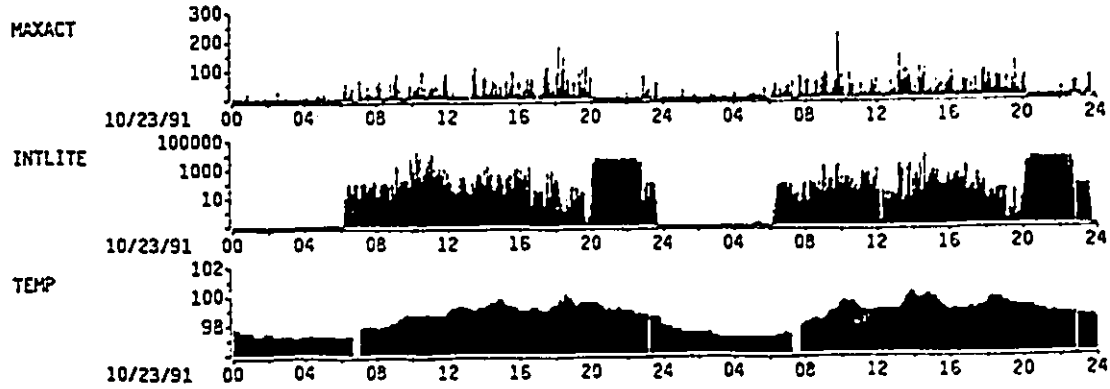


Table 6

Mean Activity Data for Each Subject in Each Experimental Condition

	Condition			
	8HBL	6HBL	ML	EL
Subject 1	20.963	22.721	18.575	18.195
Subject 2	missing	20.43	24.4	23.216
Subject 3	21.548	23.7	24.677	22.149

The activity data indicate no problems outside the laboratory. No intense physical activity was apparent (e.g., jogging or heavy physical work). Most importantly, there were no stoppages in activity that would correspond to napping.

Mean activity over each series is shown in Table 6. This measure reflects subjects' activity quite accurately because, unlike the light detector which can be covered up, the accelerometer was collecting data continuously for the entire series. The only times the Actillume was removed was for showers or to upload the information to computer. Subject 1 seemed to be slightly less active during the light conditions (ML and EL) than baseline (8HBL or 6HBL), while Subject 2 was more active during ML and EL than during the baseline (only 6HBL available). Subject 3 showed no consistent change over conditions.

The range of observations runs from 18.195 to 24.677 units. Some tests run on other subjects indicate that 24 hours of sedentary activity (e.g., office activity, walking, driving home) yield results from 18 to 25 units; while the more strenuous activities that may more easily influence body temperature (e.g., 15 minutes jogging, or cycling) can drive this up beyond 28 units. More importantly, in viewing the activity histograms, subjects never showed high levels

of activity even for brief periods. Thus, during all series, the subjects appear to have refrained from heavy exercise and napping, as requested.

Sleep Data

To establish a measure of stability for sleep, sleep stages for the first 7 hours of all 4 nights of the 8HBL condition were compared, as shown in Figure 8(a, b, c). No bright lights were used during the 8HBL. Statistical tests were not performed due to the small number of data points, so amounts of each stage, in minutes, were simply graphed for comparison. All subjects showed some minor first night effects. The only notable changes between Night 3 and the Extended night were an increase in Stage 4 and decrease in Stage 2 for Subject 1, and an increase in Stage 3 and decrease in Stage 2 for Subject 2. These data could indicate that Subjects 1 and 2 had a small increase in SWS pressure, perhaps recovery from adaptation effects. Subject 3 showed an increase in REM sleep at the expense of Stage 3. Subject 3 showed the most prominent first night effect, so this change between Night 3 and the extended night may be a slight REM rebound after SWS had been recuperated on the previous 2 nights. All subjects were within normal ranges for sleep stage amounts and patterns.

Total time spent in each sleep stage by each subject in each condition during extended sleep is shown in Table 7. In general, the amount of waking (WASO) was greatest during the 8HBL and lowest during the EL series, with the opposite being true of TST. It should be noted that WASO here also includes waking after the SWS and SWA returns, so these amounts should not necessarily be compared to late SWS and SWA. It appeared that when WASO levels were lower, WASO was replaced mainly with Stage 2 and REM. SWS levels also appeared to be highest during 8HBL and EL. REM was lowest during 8HBL, and did not differ greatly for the other

Figure 8(a): Sleep stages, in minutes, for the first 7 hours of all 4 nights of the 8HBL condition of Subject 1

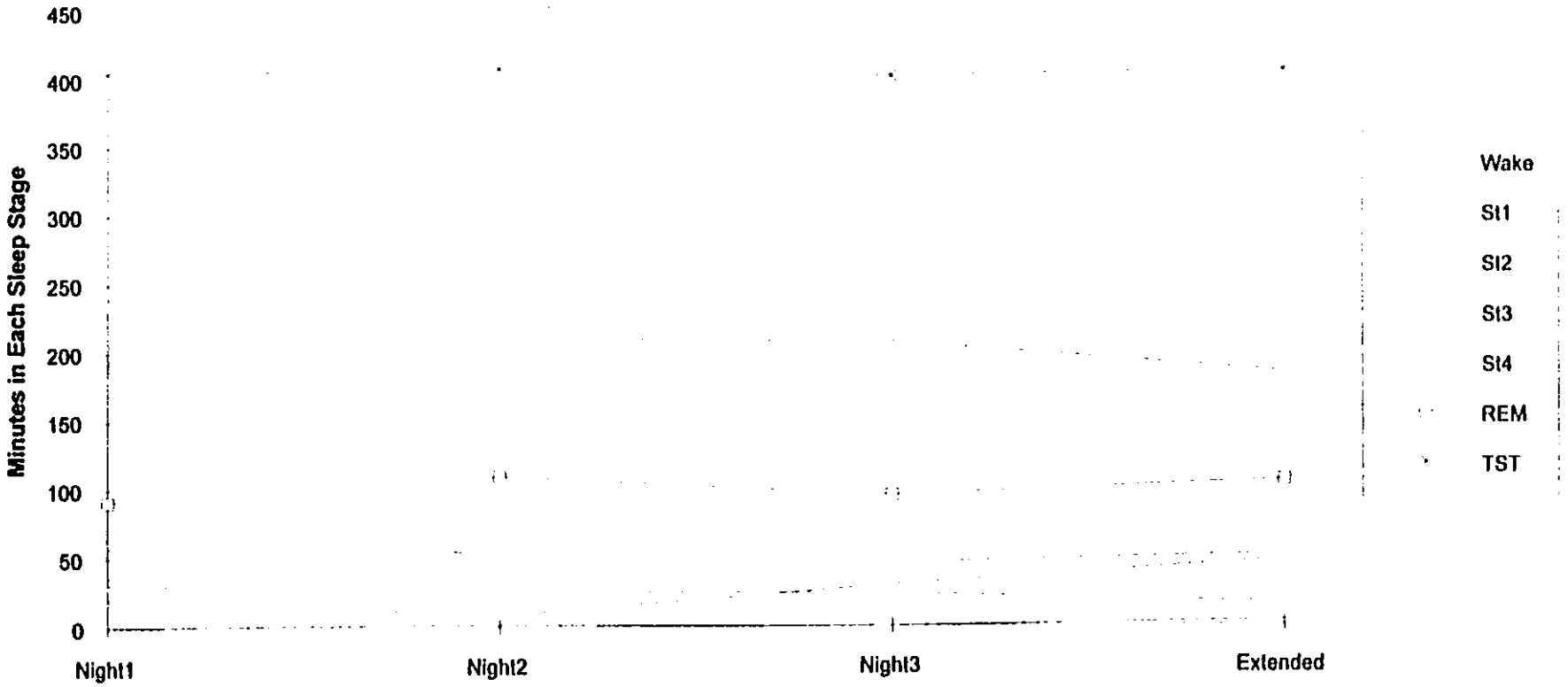


Figure 8(b): Sleep stages, in minutes, for the first 7 hours of all 4 nights of the 8HBL condition of Subject 2

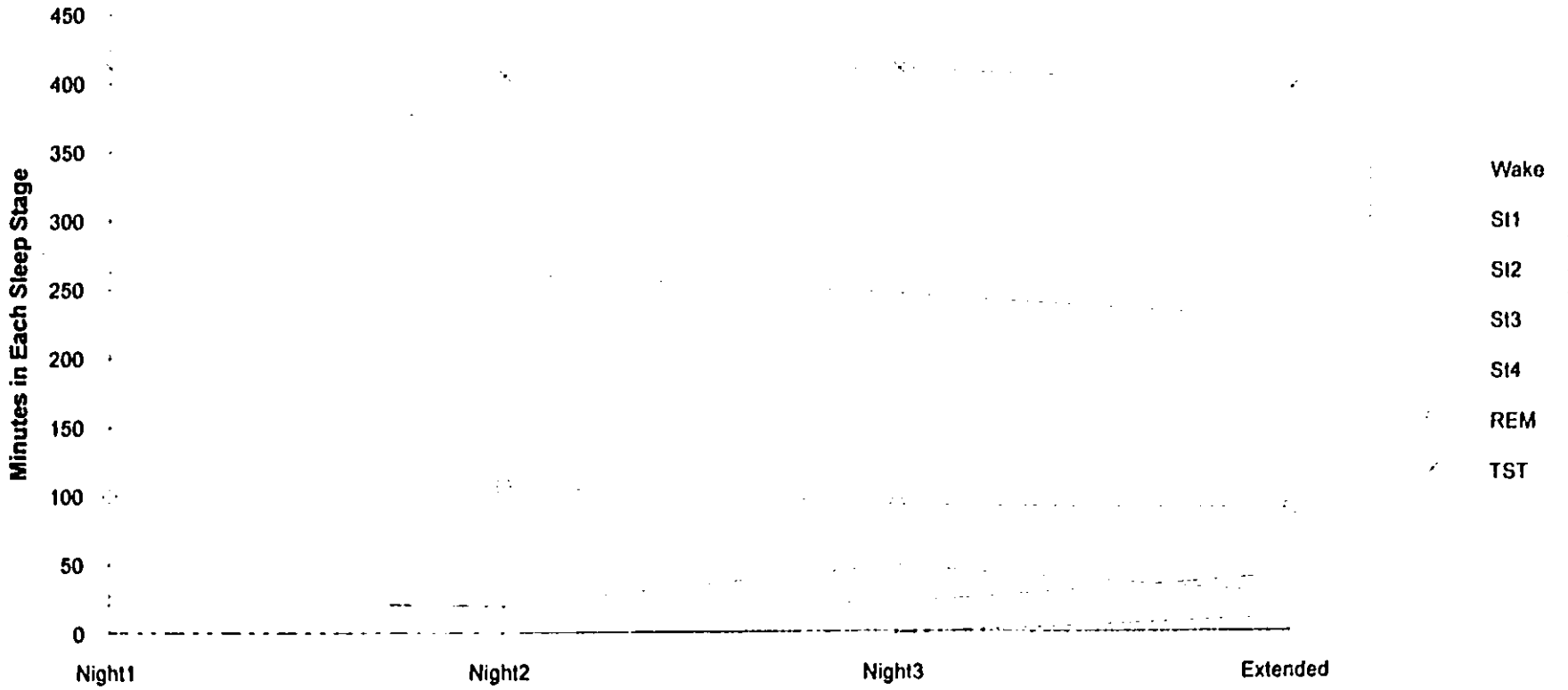


Figure 8(c): Sleep stages, in minutes, for the first 7 hours of all 4 nights of the 8HBL condition of Subject 3

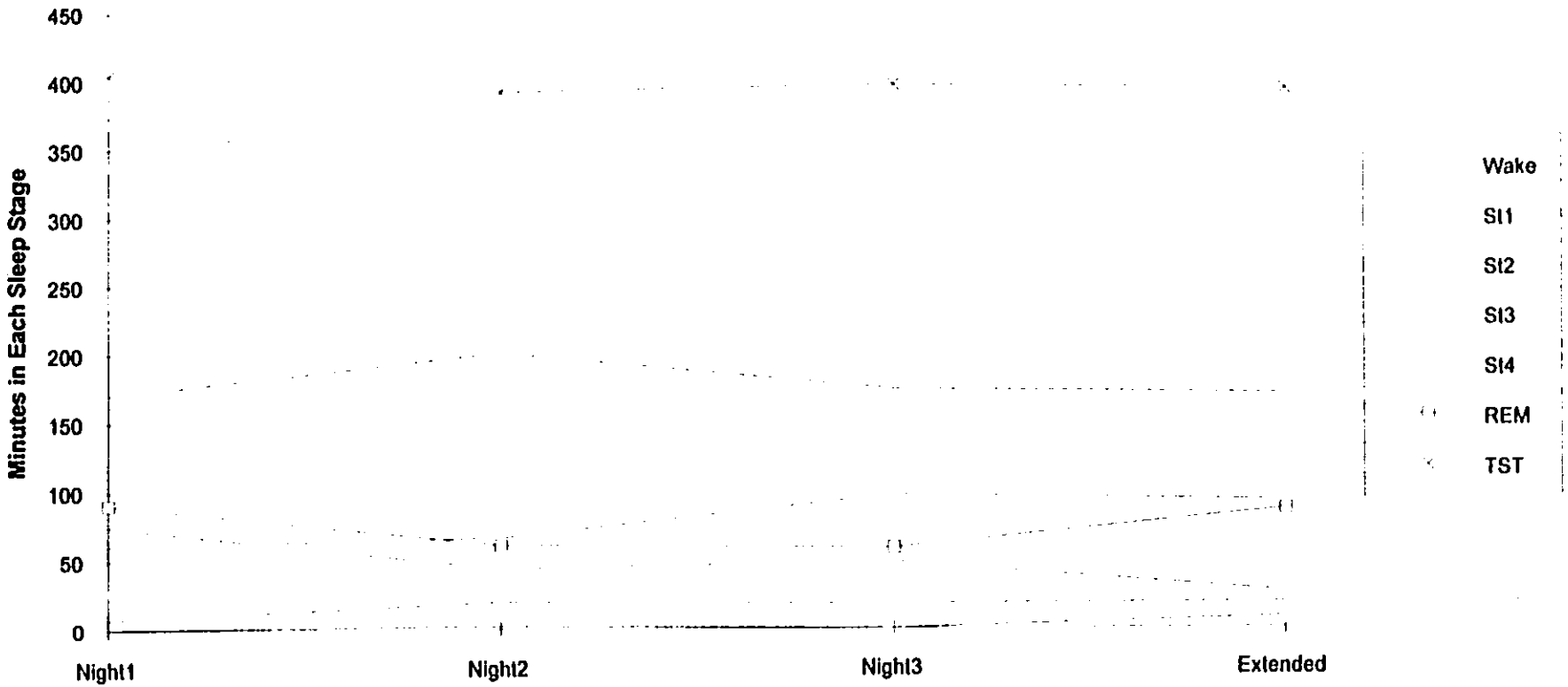


Table 7

Total time spent in each sleep stage (in minutes) by each subject in each condition during extended sleep in Study 2

	Stage							
Subject	Wake	Stage1	Stage2	Stage3	Stage4	SWS	REM	TST
Subject 1								
8HBL	160.0	116.7	306.3	66.0	49.7	115.7	167.7	706.3
6HBL	79.7	122.7	367.7	41.7	40.0	81.7	218.0	790.0
ML	144.3	148.3	308.0	38.7	52.0	90.7	160.7	707.7
EL	54.3	135.7	354.0	61.0	30.3	91.3	233.0	814.0
Subject 2								
8HBL	129.3	154.0	382.3	37.0	3.3	40.3	168.7	745.3
6HBL	48.0	147.3	406.3	50.0	6.0	56.0	214.3	824.0
ML	60.0	113.0	442.0	32.7	1.7	34.3	218.0	807.3
EL	39.0	104.3	481.0	41.3	0.3	41.7	210.3	837.3
Subject 3								
8HBL	185.7	105.0	259.3	74.0	121.3	195.3	122.7	682.3
6HBL	109.7	56.0	348.7	82.7	90.3	173.0	180.7	758.3
ML	105.0	97.0	317.7	77.0	86.7	163.7	185.3	763.7
EL	94.0	59.0	328.0	88.7	108.0	196.7	182.7	766.3

Table 8

Maximum 15 minute SWA means in the last 5 hours of extended sleep (Max_{Late}), maximum 15 minute SWA mean within 4 hours prior to Max_{Late} (Max_{Prev4}), magnitude of the SWA return, time of SWA return, and CBT phase and amplitude for Study 2.

	Measure					
Subj	Max_{Late}	Max_{Prev4}	$Return_{Mag}$	Time	CBT Phase	CBTAmp
1-8HBL	248.78	92.15	169.97	12.00	4.92	2.04
1-6HBL	139.77	163.38	-14.46	10.50	1.08	1.43
1-ML	119.75	142.02	-15.68	10.75	3.52	1.74
1-EL	146.87	233.03	-36.97	11.25	6.53	2.15
2-8HBL	183.79	86.78	111.78	11.42	1.45	3.10
2-6HBL	255.08	125.96	102.50	14.50	7.45	4.70
2-ML	103.01	89.95	14.51	12.25	5.38	2.77
2-EL	146.69	76.83	90.94	13.75	6.88	3.73
3-8HBL	236.34	138.28	70.91	14.17	(?)0.22	(?)1.35
3-6HBL	193.55	174.53	10.90	11.67	2.00	2.26
3-ML	140.36	190.30	-26.25	10.67	4.15	2.49
3-EL	173.56	96.52	79.81	12.00	7.63	2.45

Max_{Late} and Max_{Prev4} are in arbitrary units.
$Return_{Mag}$ = $(Max_{Late}-Max_{Prev4})/Max_{Prev4}*100$
Time = time from sleep onset to Max_{Late} in hours
CBT Phase = time from sleep onset to CBT minimum in hours
CBT $amplitude_{ch}$ = CBT drop + rise during sleep in degree Fahrenheit
(?) = CBT was not used in calculation due to artifact

conditions (except subject 1, ML), likely a result of more disruption late in the sleep period.

The time course of SWA, sleep stages, and CBT data for each condition (8HBL, 6HBL, ML, and EL) for subjects 1, 2, and 3 are shown in Figures 9, 10, and 11 respectively. It can be seen that there are increases in SWS and SWA in the final 3 hours of several of the conditions. Table 8 shows presence cr absence of a SWA return, as well as timing and magnitude of the return. The SWA return is defined as in Study 1, relative to the previous 4 hours (see p. 44). Also

Figure 9(a): CBT, sleep stage,
and SWA (power) data for Subject 1 in Study 2 (8HBL)

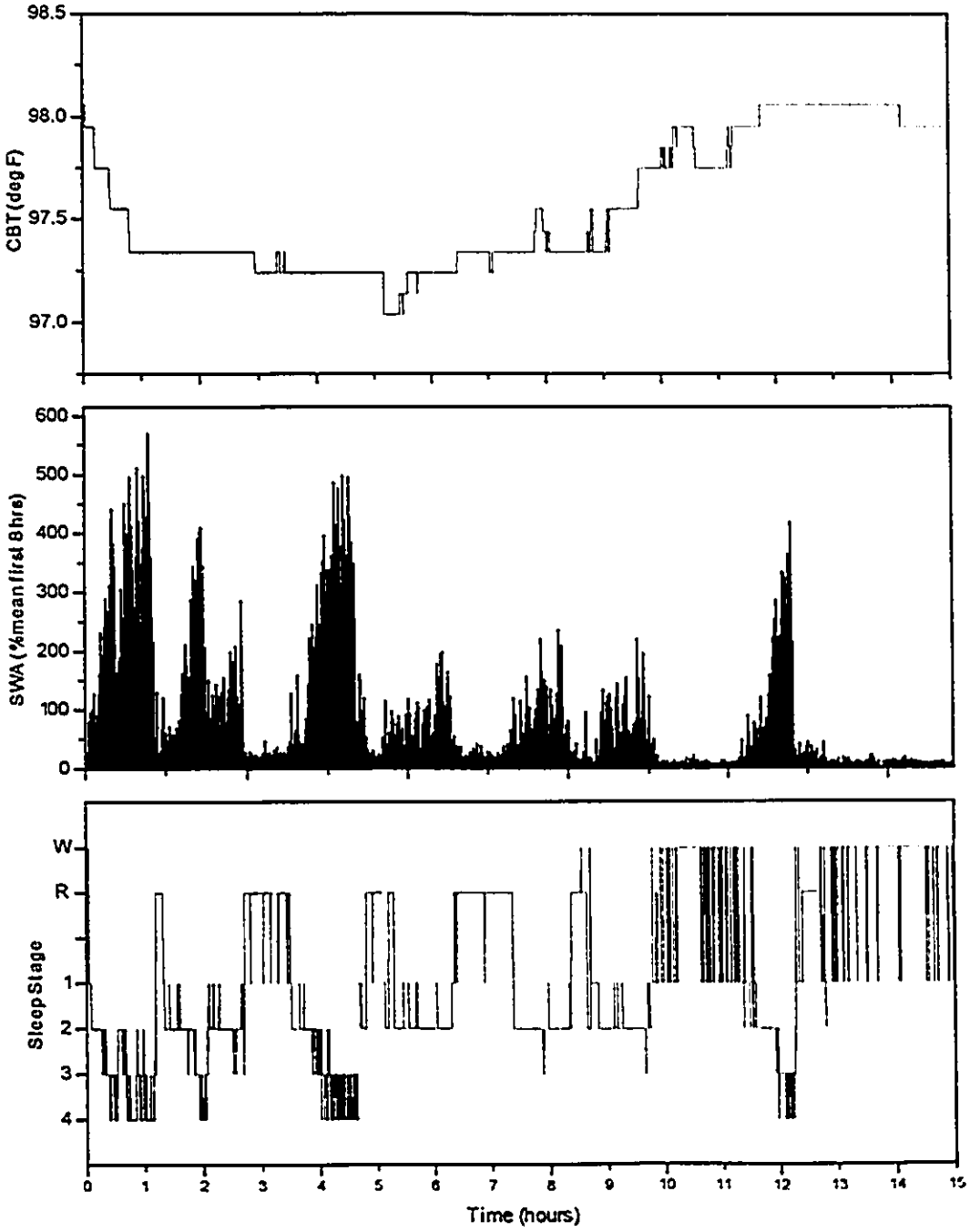


Figure 9(b): CBT, sleep stage,
and SWA (power) data for Subject 1 in Study 2 (6HBL)

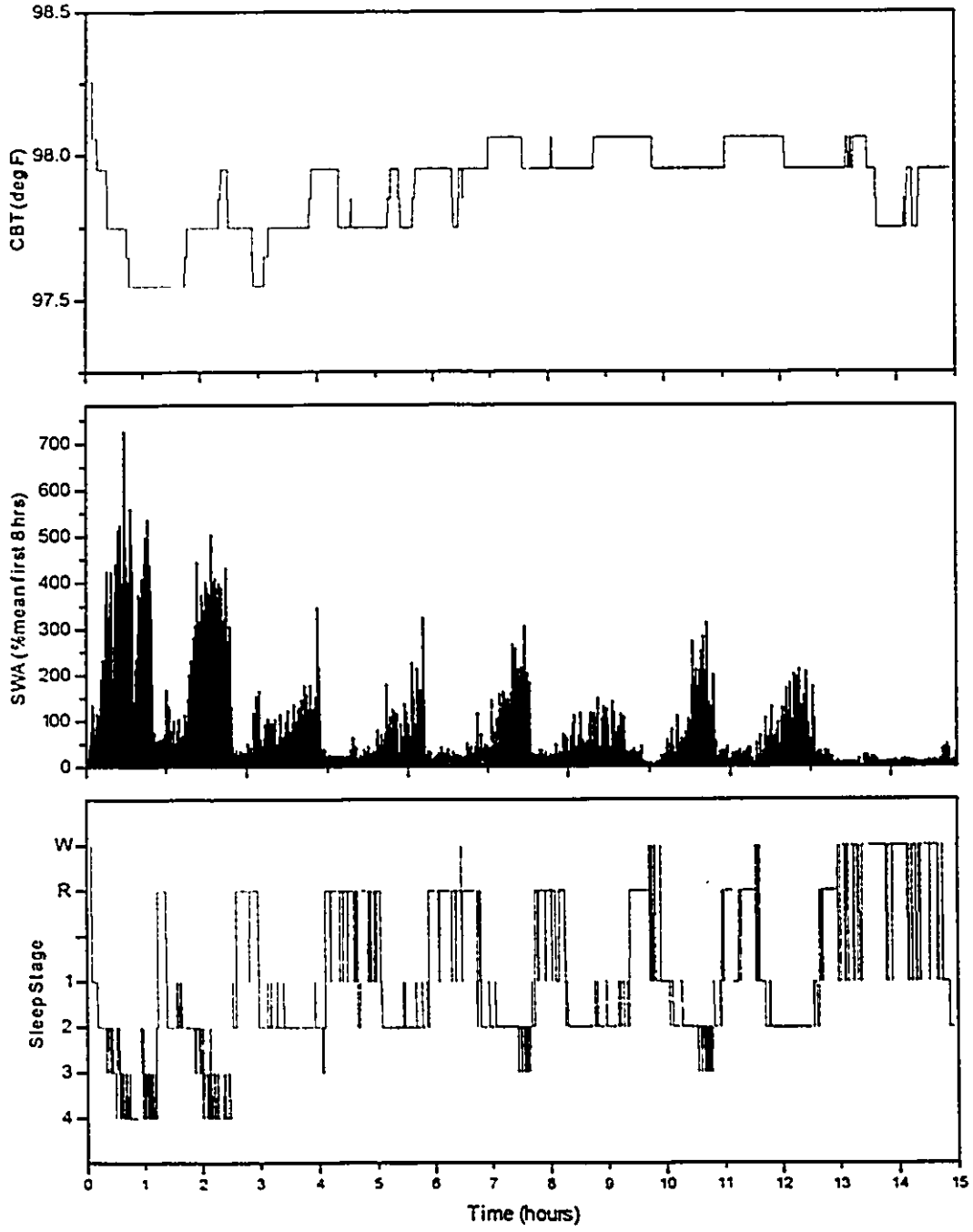


Figure 9(c): CBT, sleep stage,
and SWA (power) data for Subject 1 in Study 2 (ML)

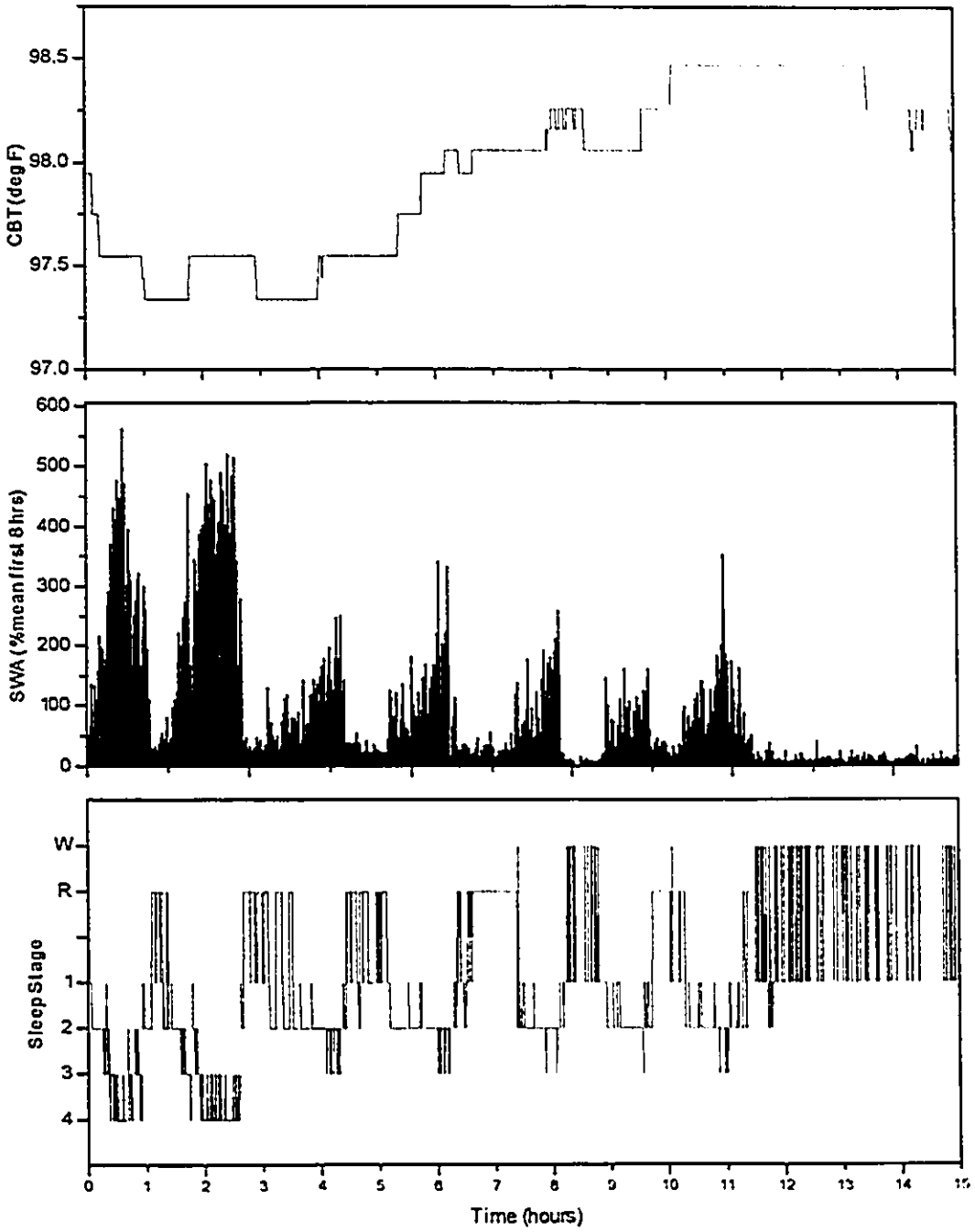


Figure 9(d): CBT, sleep stage,
and SWA (power) data for Subject 1 in Study 2 (EL)

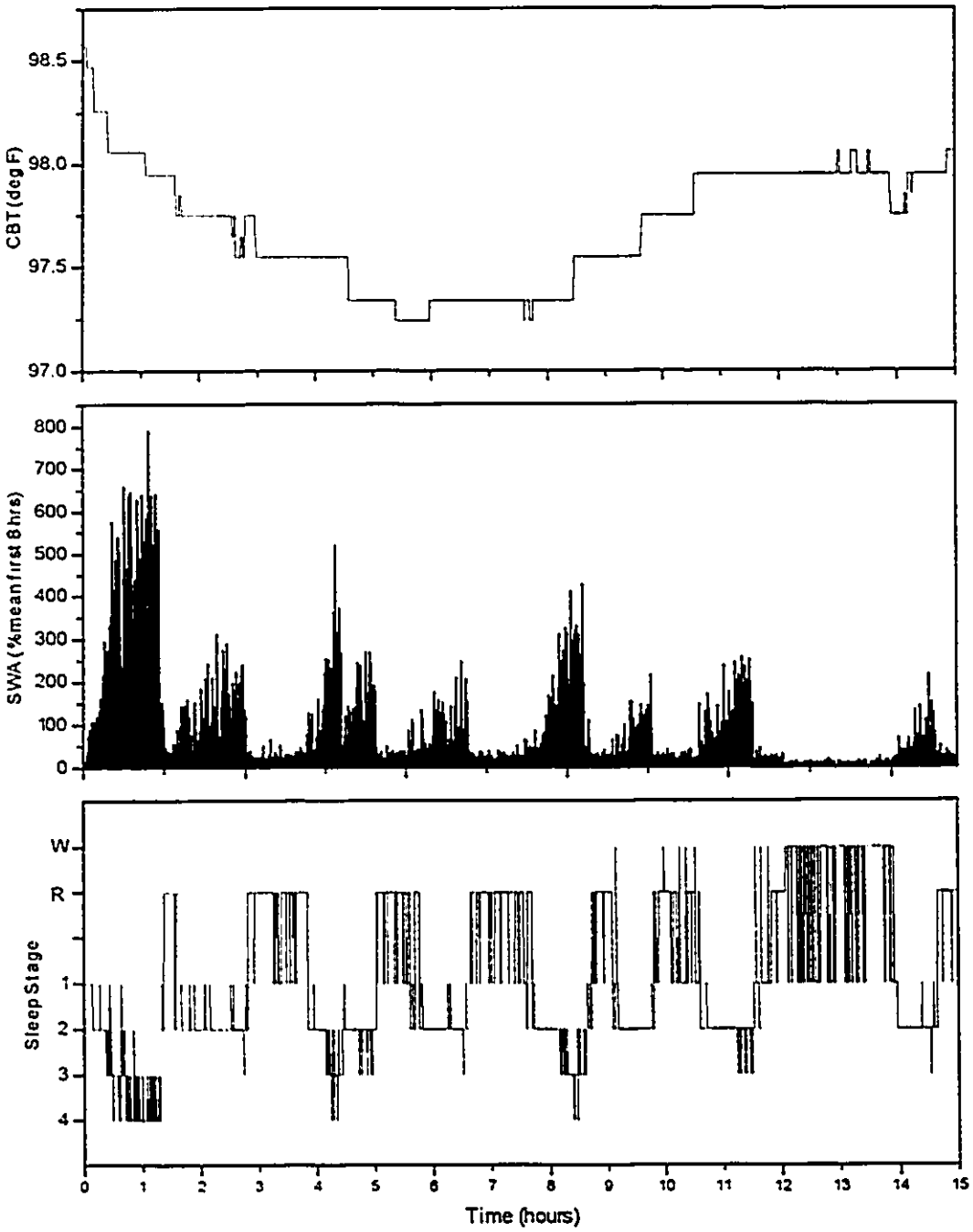


Figure 10(a): CBT, sleep stage,
and SWA (power) data for Subject 2 in Study 2 (8HBL)

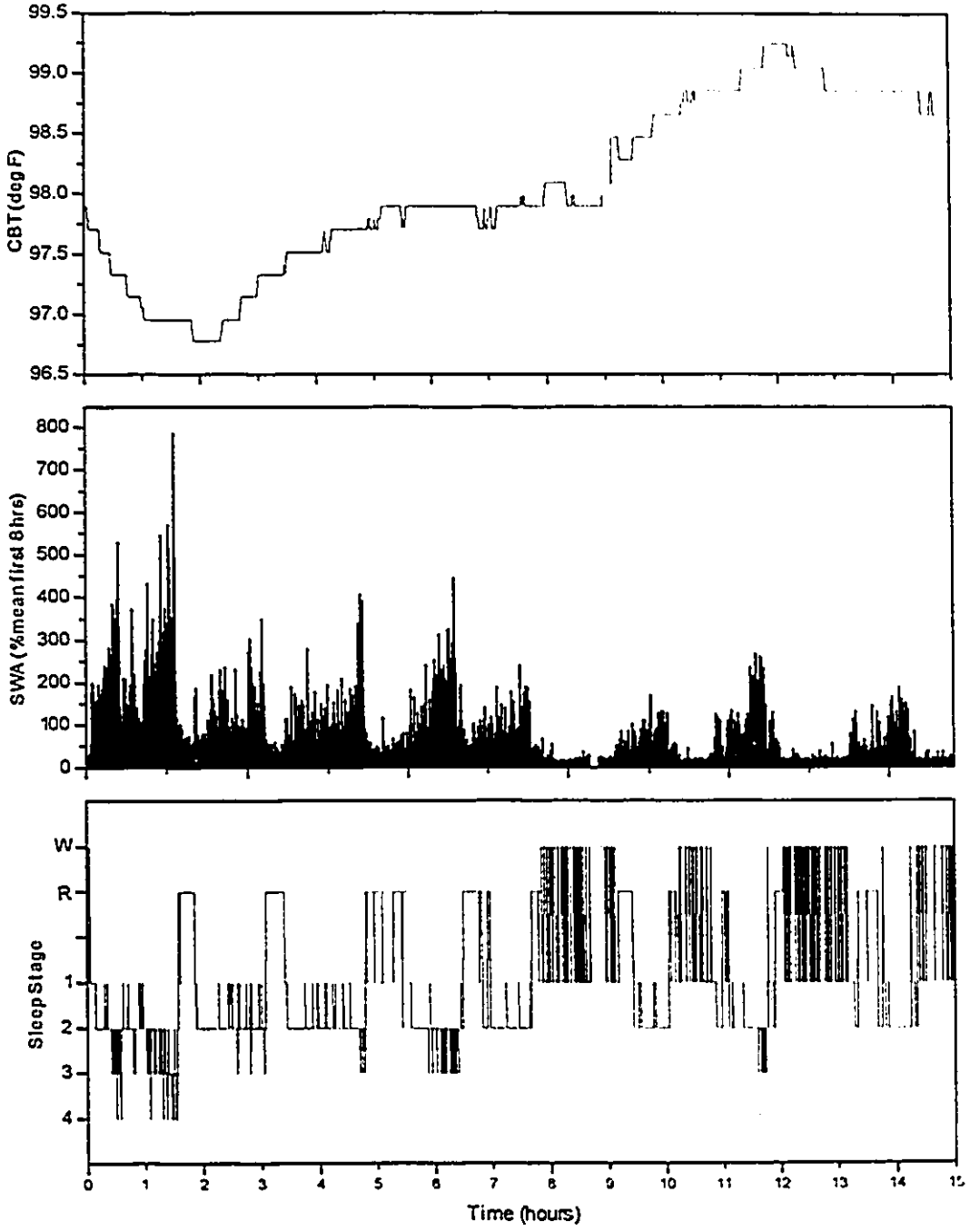


Figure 10(b): CBT, sleep stage,
and SWA (power) data for Subject 2 in Study 2 (6HBL)

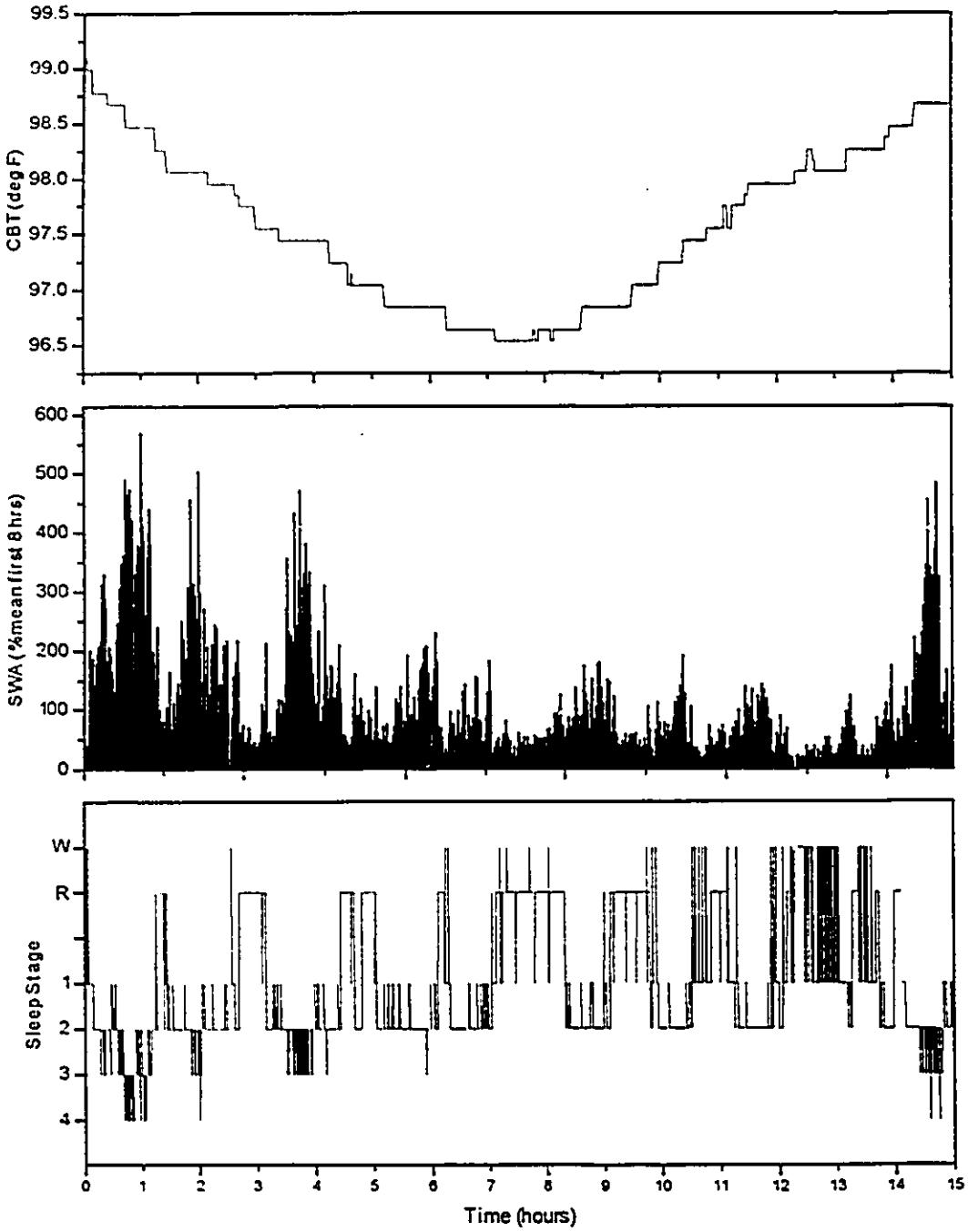


Figure 10(c): CBT, sleep stage,
and SWA (power) data for Subject 2 in Study 2 (ML)

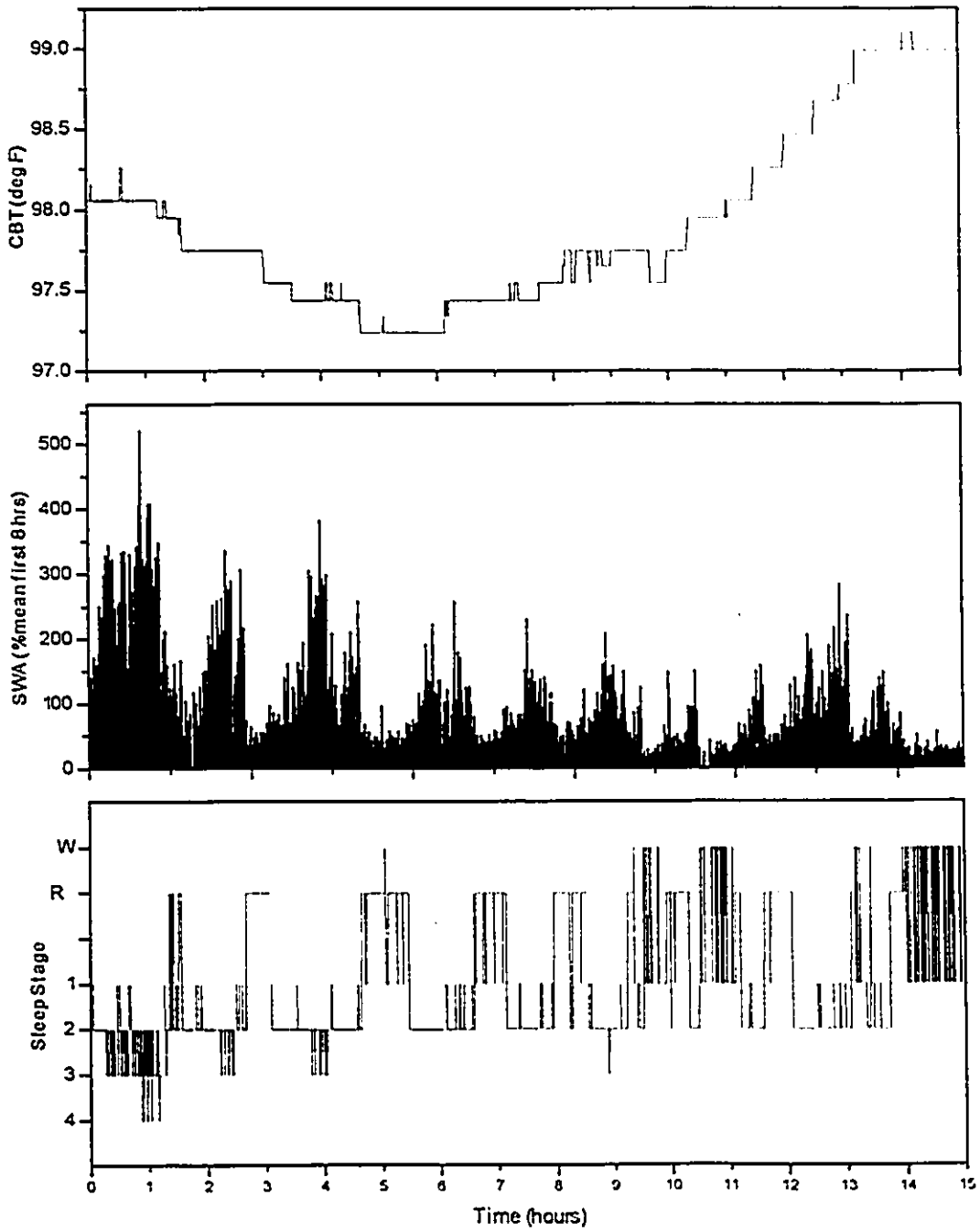


Figure 10(d): CBT, sleep stage,
and SWA (power) data for Subject 2 in Study 2 (EL)

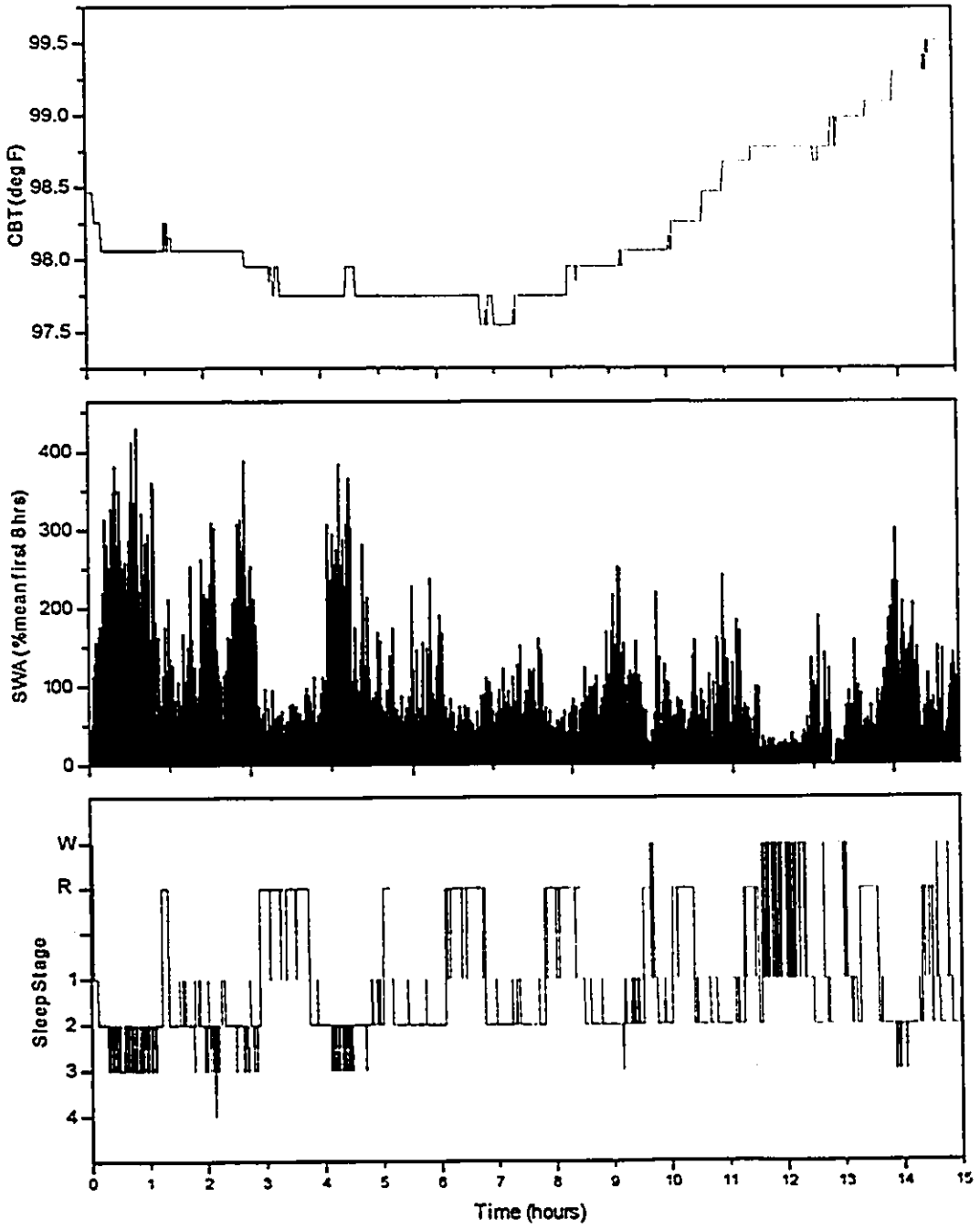


Figure 11(a): CBT, sleep stage,
and SWA (power) data for Subject 3 in Study 2 (8HBL)

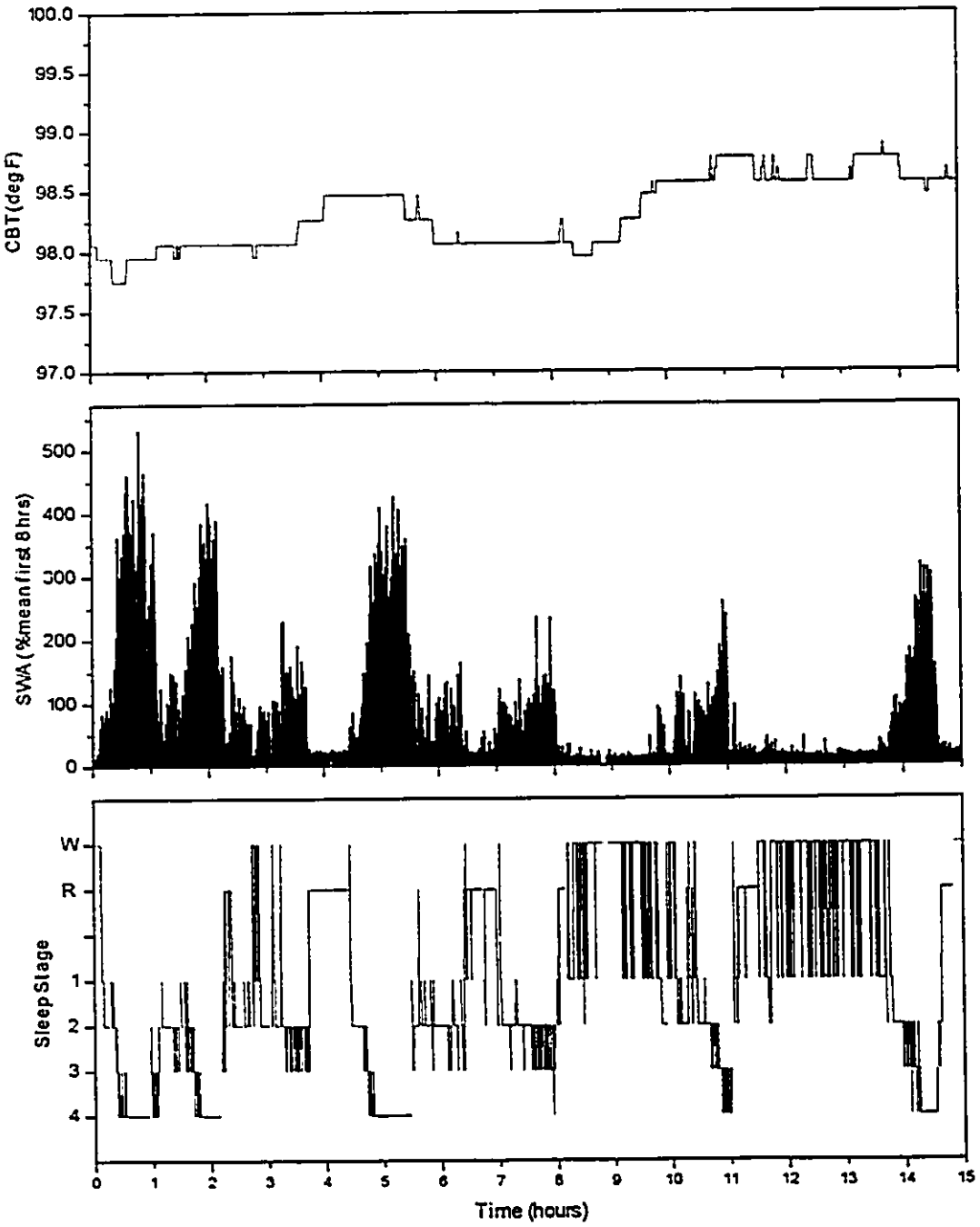


Figure 11(b): CBT, sleep stage,
and SWA (power) data for Subject 3 in Study 2 (6HBL)

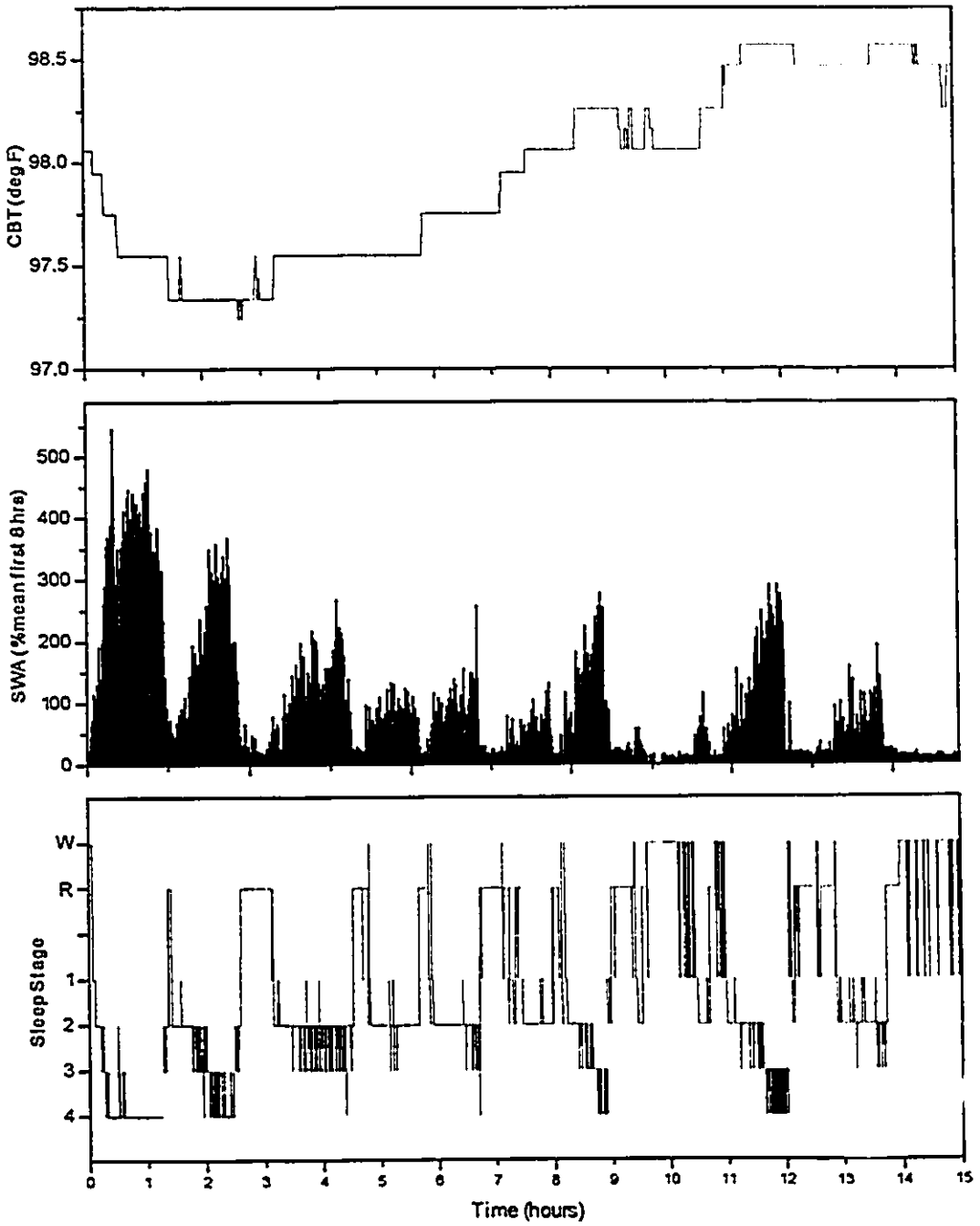


Figure 11(c): CBT, sleep stage,
and SWA (power) data for Subject 3 in Study 2 (ML)

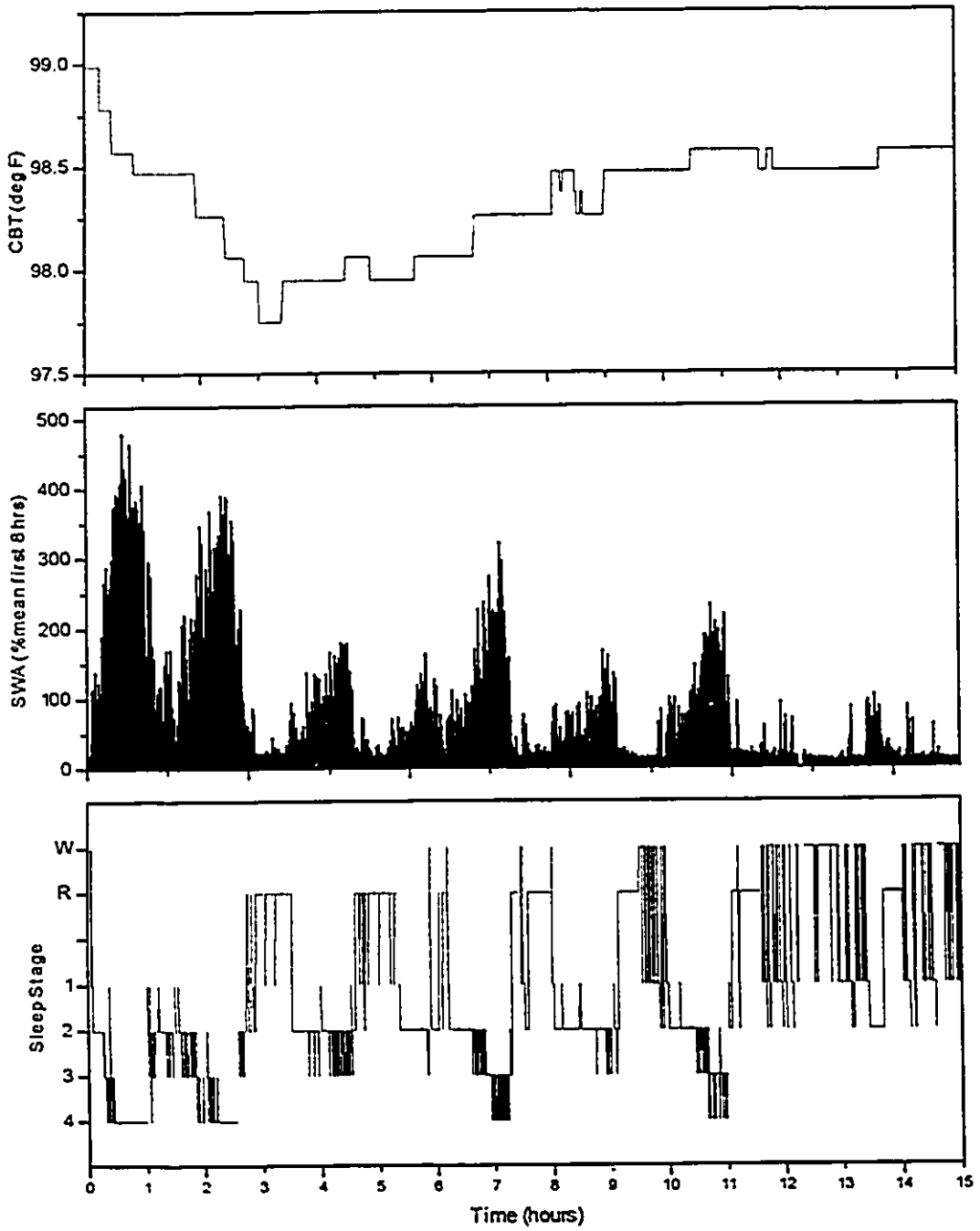
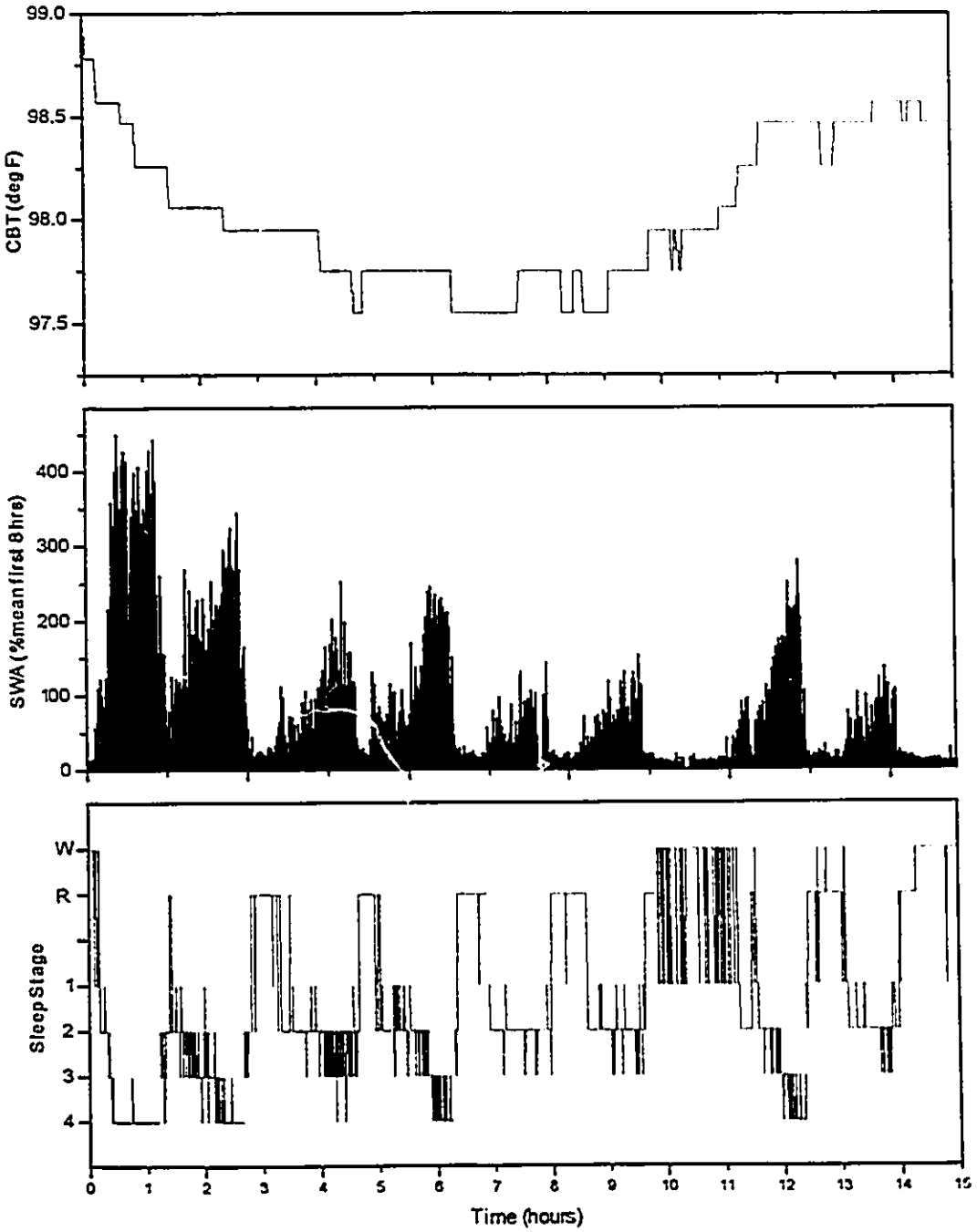


Figure 11(d): CBT, sleep stage,
and SWA (power) data for Subject 3 in Study 2 (EL)



presented in Table 8 are CBT phase, determined as in Study 1 with a 9th degree polynomial (see Appendix 2 for fitted curves).

The data will be examined with respect to the late SWS and SWA first, then to the CBT changes during the different bright light conditions, and finally to the changes in SWS and SWA associated with those CBT changes.

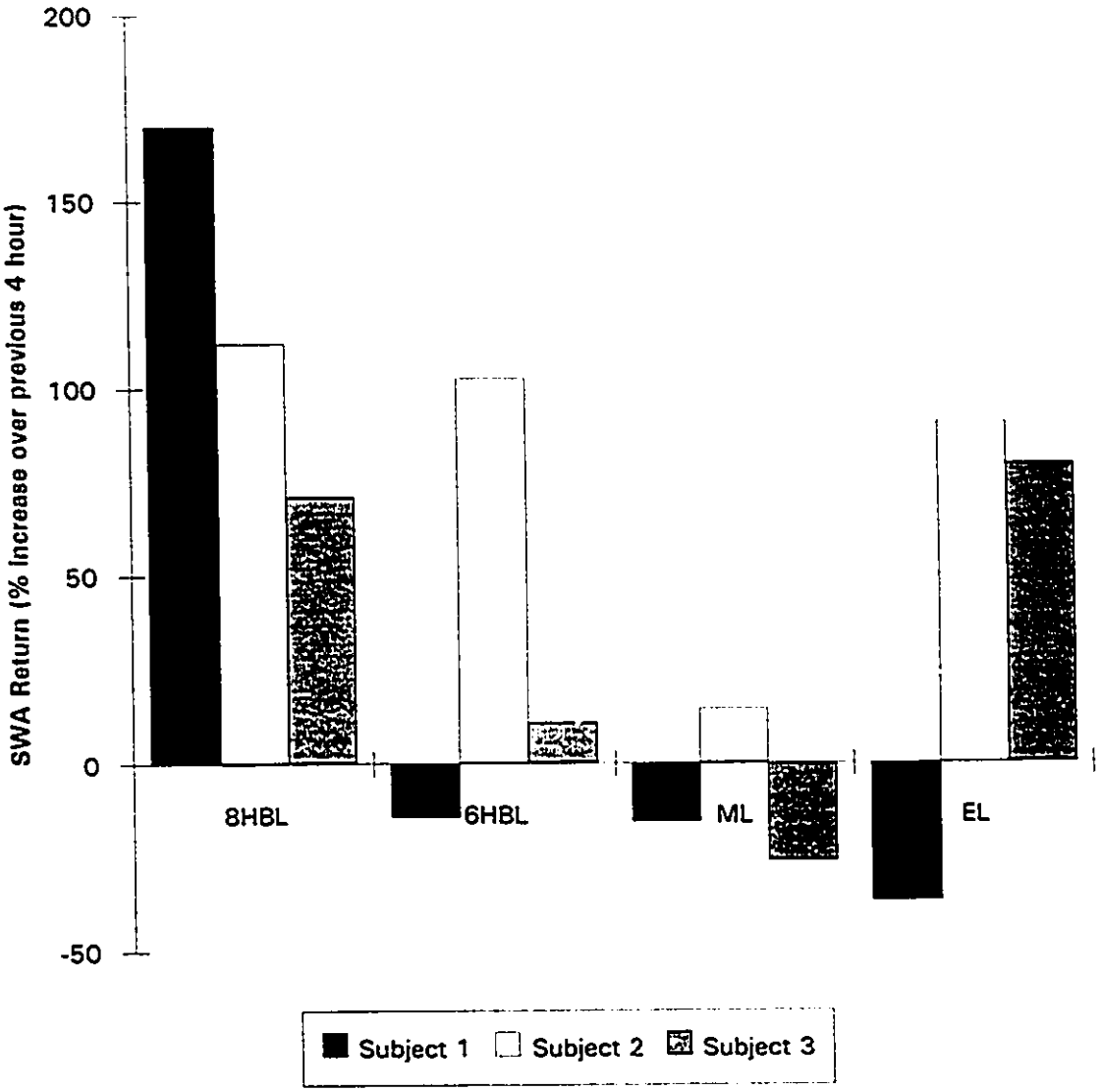
Late SWS and SWA

Figures 9, 10, and 11 show that many of the experimental conditions had episodes of SWS and high SWA in the last 5 hours of sleep. However, as was mentioned in Study 1, this may reflect more a persistence of SWS and SWA than a return. Since the magnitude and timing of SWA returns better reflect the time course of SWA, they were examined in the most detail. These SWA measures are shown in Table 8, and magnitude of SWA return is presented in relation to each experimental condition in Figure 12.

During the 8HBL, all subjects showed a SWA return. These returns were at least 71% greater than the maximum 15 minute average during the previous 4 hours. During the 6HBL, subject 1 showed no return, subject 2 a marked one (102.5%), and subject 3 a small one (11.9%). The ML condition showed less late SWA, with subjects 1 and 3 having no return, and subject 2 showing a small return (14.5%). During EL, subject 1 showed no return, with very low late SWA (37% lower than the maximum in the previous 4 hours), and the other two subjects showed large returns (90.9% for subject 2, and 79.8% for subject 3).

All subjects showed a return of SWA during 8HBL, so the phenomenon of a SWA return was present in all of them. However, the SWA returns varied somewhat differently for each subject across conditions. Subject 1 showed no return during all other conditions, with approximately equal values during 6HBL (-14.5%) and ML (-15.7%), and very low SWA

Figure 12: SWA return magnitude for each subject in each condition of Study 2



during EL (-37%). Subject 2 had a return in all conditions, showing relatively small differences between the 8HBL (111.8%), 6HBL (102.5%), and EL (90.9%) conditions, with ML having a sharp drop to 14.5%. Subject 3 had a small return during 6HBL (10.9%), no return during ML (-26.2%), and his largest return during EL (79.8%).

In general, highest SWA returns were during 8HBL and EL (with the exception of subject 1), and lowest levels during ML. The 6HBL was mixed, with one subject high and the other two low. This variability may be clarified by looking at the changes in CBT phase during each condition.

CBT and Bright Light

As shown in Table 8, CBT phase, expressed as delay from sleep onset to CBT minimum, did not shift exactly as planned. In subject 1, the desired phase advance during ML (+84 minutes) and phase delay of EL (-97 minutes) did occur relative to 8HBL (0). However, there was a large phase advance (+230 minutes) during 6HBL. With subject 2, the two baselines differed greatly, but with all conditions phase delayed relative to 8HBL (0), with 6HBL delayed the most (-360 minutes). The CBT minimum for EL (-326 minutes) occurred 90 minutes after the ML (-236 minutes). Subject 3 showed phase delays in all conditions (-107 minutes for 6HBL, -236 for ML, and -445 for EL) relative to the 8HBL. Again, the EL was phase delayed (-209 minutes) relative to ML.

With subject 3 it should be noted that the CBT curve for the 8HBL showed an unusual peak about 5 hours after sleep onset, with a second decline afterward. The curve appears to have 2 minima, the first being the lowest. This observation was likely artifact, since previous nights and all nights in other conditions for this subject showed a decline then rise with a single minimum. The second of the two minima on the extended night, although not the lowest

CBT, was closer to the timing of minima on preceding nights. Thus this night had to be viewed with caution, so it was excluded from calculations involving CBT.

In all cases, ML was phase advanced relative to EL. The 8HBL and 6HBL, however, behaved unexpectedly, all being phase advanced relative to both light conditions, with two exceptions: the 6HBL for subject 2 was phase delayed relative to light conditions, and the 8HBL for subject 1 which occurred between the ML and EL times as was predicted. Neither light condition for subject 1 showed a SWA return, so the CBT shifts could not readily be compared to corresponding SWA return shifts.

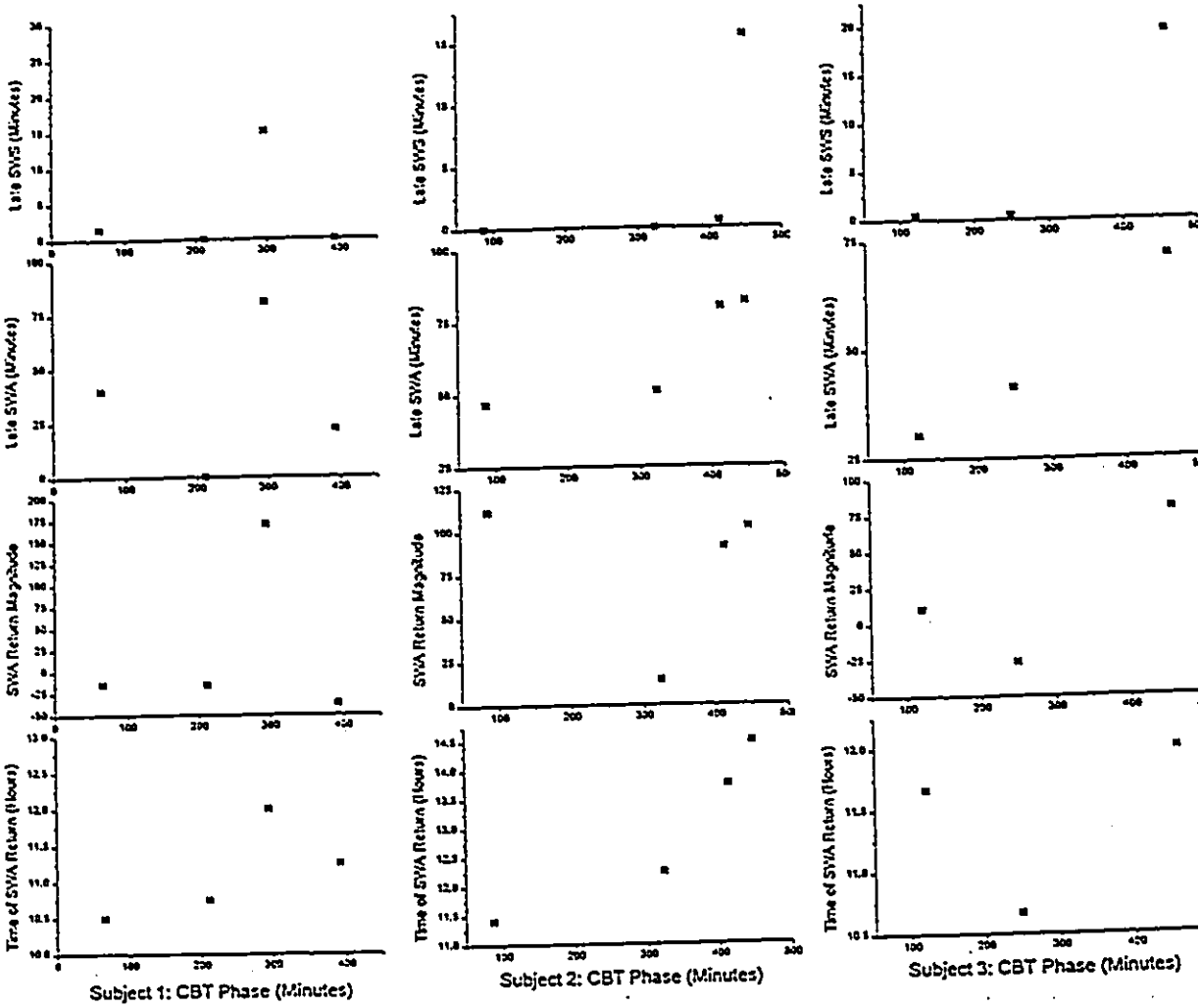
Since the CBT minimum for EL conditions were always phase delayed relative to ML conditions (-181, -90, and -209 minutes), and with the 8HBL and 6HBL also at different times, there are observations from a variety of CBT phases for each subject. So the changes in CBT phase can be compared to late SWS and SWA to examine the relationship, despite the unanticipated CBT phase shifts.

CBT and Late SWS and SWA

Since the sample size was too small for detailed statistical analysis, the relationships of CBT to SWS and SWA were examined using graphs. Figure 13 shows the relationships between CBT phase and SWS or SWA in the last 3 hours, magnitude of SWA returns, and timing of SWA (or Max_{Late} in subjects with no return) for each subject.

For Subject 1 (Figure 13), there appeared to be no relationship between CBT phase and late SWS, with SWS levels very low for 3 conditions and higher for one. This would be expected since only one condition (8HBL) showed a large SWS/SWA return. Late SWA also showed basically no relationship to CBT phase. For SWA return magnitude, the data resembled those of late SWS, with 3 low data points and 1 high. However, the CBT phase showed a positive

Figure 13
CBT phase plotted against SWS and SWA in the last 3 hours, magnitude of SWA returns, and timing of SWA returns (or Max_{Late}) for each subject.



relationship to timing of SWA return.

Subject 2 (Figure 13) also showed no relationship of CBT phase to late SWS. However, there was a tendency for a positive relationship of CBT phase to late SWA. This was the subject who showed very little SWS by visual scoring, but who showed returns of SWA when spectral analysis was used. The data for the magnitude of the SWA return showed no relationship to CBT phase, with the 3 conditions that had a SWA return showing approximately the same magnitude (ML had the low return). But again for the CBT phase and timing of SWA return data, there was a positive relationship.

For Subject 3 (Figure 13), it was more difficult to note relationships because, as mentioned earlier, the CBT data for the 8HBL was not included. But from the 3 conditions that remain, CBT phase showed slight positive relationships to late SWA, and a weaker one to late SWS.

So overall, the strongest relationship appeared to be a positive association between CBT phase and timing of SWA return (but not in Subject 3). There was also a tendency toward a positive relationship between CBT phase and late SWA (but not in Subject 1). Of course these relationships are only from visual inspection, so should be seen as tentative.

Pooled Data From Study 1 and Study 2

When the data from Study 1 were combined with the 8HBL series of Study 2, which had comparable conditions, the relationships between CBT phase and sleep parameters may be examined with more certainty.

SWA Return

A matched pairs t-test between the maximum 15 minute SWA average during the last 5 hours (Max_{Late}) and the same such maximum for the preceding 4 hours (Max_{Prev4}), for all subjects, showed that the SWA return was significant ($t=2.969$, $df=9$, $p<.01$, 1-tailed).

Relationship of WASO and REM to Late SWS or SWA

Since WASO and REM both were correlated to the same SWS and SWA measures, the alpha level of $p<.05$ was halved to give a level of $p<.025$ for significance. One-tailed tests were used. The measure of WASO+REM was not included since it had been not been significant in Study 1, and would only reduce the power of the test.

For all subjects, WASO and REM were not significantly correlated with SWS in the last 3 hours ($r_s=.517$, df=8, $p>.05$ and $r_s=-.225$, df=8, $p>.05$, respectively). WASO and REM were not significantly correlated to late SWA either ($r_s=.442$, df=8, $p>.05$ and $r_s=-.006$, df=8, $p>.05$, respectively).

When looking at magnitude of SWA returns, including cases where this was negative, WASO and REM were again not significantly related to the magnitude of the SWA return ($r_s=-.164$, df=8, $p>.05$ and $r_s=.152$, df=8, $p>.05$ respectively).

This indicated that the late SWS and SWA, as well as the magnitude of the SWA return were independent of WASO and REM, supporting the notion that other factors were important in determining the course of SWS and SWA.

Relationship of CBT to SWS or SWA

There was a significant association between CBT phase ($r_s=.695$, df=7, $p<.03$) to SWS in the last 3 hours of sleep. There was not a significant relationship of CBT phase to SWA in the last 3 hours of sleep ($r_s=.433$, df=7, $p>.05$). As mentioned earlier, CBT data for subject 3 was not used in calculation, so $n=9$.

Magnitude of SWA return had a significant relationship to CBT phase ($r_s=.700$, df=7, $p<.03$). CBT phase also had a significant positive relationship to timing of SWA maximum in the last 5 hours, Max_{Late}, ($r_s=.644$, df=7, $p<.05$). Thus there appears to be a relationship between the magnitude and

timing of highest SWA levels in the last 5 hours and CBT phase.

Discussion of Results

When interpreting the results of these studies, it must be kept in mind that the sample size was relatively small (n=7 for Study 1, and n=3 for Study 2), so findings should be viewed with due caution. The results will be summarized and discussed first with reference to each prediction, then general comments will follow.

Study 1: Prediction 1

There should be a return of EEG SWS (detected by visual scoring) approximately 12.5 hours after sleep onset. This return of SWS should be unrelated to intervening WASO, REM or WASO+REM sleep amounts.

Prediction 1 was confirmed, but the SWS return was not a large effect, and was not present in all subjects. The results supported the notion of a 12-hour rhythm of SWS (Broughton, 1975; 1988). It could also be argued, under the revised 2-Process Model (Achermann, Beersma, and Borbély, 1990), that Process S builds up during sleep such that after 12 hours of sleep, there is a new pressure for SWS, but this would involve more than just WASO and REM (and would make it basically equivalent to a 12-hour rhythm).

Study 1: Prediction 2

There should be a similar return of SWA (as measured by spectral analysis) after 12.5 hours, also not related to WASO, REM or WASO+REM sleep.

Prediction 2 was confirmed. The results indicated that levels of SWA did increase significantly toward the end of extended sleep, but this increase only approached significance for the magnitude of the SWA return as defined by the 15 minute averages.For subjects exhibiting a SWA return, the delay to return was longer than 12.5 hours in all cases (average of 13.8 hours).

Study 1: Prediction 3

There should be a relationship between CBT and magnitude of the SWS/SWA return. Either circadian phase of CBT, or perhaps magnitude of CBT change should be related to SWS/SWA return. More specifically, the CBT rhythm should have a stable phase relationship to the postulated 12-hour rhythm of SWS/SWA. Consequently, CBT phase should have a positive relationship with the SWS/SWA return magnitude and timing.

The prediction of a positive relationship between CBT phase to timing of SWS/SWA return was not confirmed in Study 1 alone, although it approached significance. However, the prediction of a positive relationship to SWS or SWA return was confirmed for late SWS and magnitude of SWA return, but not for late SWA.

As noted earlier, there was also a significant association between CBT phase and CBT $amplitude_{ch}$, likely related to longer CBT delay to minimum allowing greater CBT drop before the same rise to CBT maximum that would occur with shorter delays to CBT minimum. So if CBT phase has an association with SWS or SWA, then the CBT $amplitude_{ch}$ of change is likely to as well.

Study 1: Prediction 4

Presuming that SWS/SWA plays some role in thermoregulation, the reappearance of EEG SWA will be accompanied by a drop in CBT.

Although CBT sometimes reached a maximum and began to drop again before the end of the 15 hour recording period, there appeared to be little relationship with SWS or SWA. If SWA were important for thermoregulation, the cross correlation between CBT slope and SWA should have shown this relationship. Cross correlations between CBT slope and SWA, over the whole extended sleep or just the last 5 hours (when the SWA returns occurred) showed no consistent relationship. The late SWS and SWA episodes were not observed to be accompanied by CBT decreases. Thus, Prediction 4 was not

confirmed.

Study 2: Prediction 1

There should be a return of EEG slow wave activity (detected by visual scoring, and spectral analysis) approximately 12.5 hours after first appearance of SWS. This return of SWA should be unrelated to intervening WASO and/or REM sleep amounts.

There were late increases in SWA during some conditions, and not others. All subjects showed a SWA return, based on the 15 minute running averages, during the 8HBL condition. So each subject was capable of a SWA return. However, results were more variable during other conditions, some with SWA returns and some without (8 out of 12 conditions showed some SWA return). During 8HBL, the SWA returns were a mean of 12.5 hours after sleep onset; however, 2 were actually less than 12.5 hours.

To investigate relationships of WASO, REM, and WASO+REM to late SWS, late SWA, or magnitude of SWA return, the 8HBL conditions were combined with the data from Study 1, which had comparable conditions. No significant relationships were found. Also, with this pooled data, the increase in SWA during the return was significant.

Study 2: Prediction 2

Morning bright light will phase advance the CBT rhythm, and evening bright light will phase delay the CBT rhythm.

Prediction 2 was confirmed in that ML conditions showed CBT phase advances relative to EL conditions in all cases. This prediction was not confirmed in that 8HBL and 6HBL CBT minima, the phase marker, did not occur between those of ML and EL. The 8HBL, and 6HBL did, however, give other phase relationships between CBT and SWS or SWA for comparison.

Perhaps longer periods of bright light (4-5 hours instead of 3 hours) would have had a larger effect on CBT phase. Placing the bright light periods closer to the CBT minimum may also have increased the CBT shifts, but this

would also have caused more sleep restriction if sleep timing was to be kept the same in all conditions. The lights were already quite bright, so raising light intensity to increase CBT shifts may not have been recommendable.

Study 2: Prediction 3

The phase advance in CBT rhythm will be accompanied by an advance in the return of EEG SWA, and a phase delay in CBT rhythm will be accompanied by a delay in the return of EEG SWA.

Study 2 gives data with different phase relationships of sleep timing to CBT rhythm within subjects, while keeping prior wakefulness constant. So the only differences within subjects should have resulted from CBT rhythm changes. The data in Figure 13 show that there appeared to be a relationship between CBT phase to timing of SWA return in 2 out of 3 subjects (not in Subject 3), as well as between CBT phase and late SWA, also in 2 of the 3 subjects (not in Subject 1). Since these relationships were from visual inspection only, their significance is debatable. But from these data, Prediction 3 was confirmed in 2 of 3 cases.

To further investigate the link between CBT to timing of SWA return, the data from the two 8HBL conditions with CBT data (Subject 3 omitted) and the data from Study 1 were pooled. These data showed there were significant relationships between CBT phase and timing of the maximum SWA in the last 5 hours (Max_{Late}, 7 of 9 were SWA returns), supporting Prediction 3 from Study 2, and Prediction 3 from Study 1. These pooled data also revealed significant relationships of CBT phase to late SWS, and magnitude of SWA return, with CBT phase to late SWA being non-significant.

CBT rhythm does seem to be associated with the timing of the highest levels of SWA in late sleep, whether they exceed previous levels or not. This may indicate a coordination between CBT rhythm and SWS/SWA pressure.

Perhaps CBT relates to windows when SWS and high SWA are more likely.

Differences between the measures of SWS and SWA

SWS and SWA measures certainly reflected one another, however, they did show differences. In Study 2, Subject 2 showed very little SWS in general, and almost none late in extended sleep. However, when the data were analyzed for SWA, this subject showed SWA returns in all conditions, indicating the added information that power spectral analysis can give.

Interpretation of Results

According to our findings, there were late increases in SWS and SWA during extended sleep, that were not significantly related to WASO, REM or WASO+REM, which runs counter to the 2-Process Model (Daan, Beersma, and Borbély, 1984). In defence of Process S, it must be noted that although non-significant, correlations of SWS or SWA returns showed positive relationships with WASO, but almost no relationship to REM. This independence from REM does not support the idea of Horne (1988) that REM also increases SWS and SWA pressure. The concept of Process S has much validity, but the special conditions of extended sleep indicate that prior waking alone does not account for the time course of SWS and SWA beyond 12 hours. The amount of SWS and SWA in the final 3 hours is only a small portion of the total SWS and SWA for the entire sleep period (9.5% of total SWS, and 17.2% of SWA in Study 1). But the fact that several studies have shown SWS or SWA after 12 hours of sleep suggests that this may be a small but, nevertheless, robust phenomenon that must be addressed.

Over the 10 subjects in Studies 1 and 2, 8 showed a SWA return. These SWA returns occurred between 12.0 hours and 14.83 hours after sleep onset, with a mean of 13.35 hours. This variation in magnitude and timing of late SWA episodes,

and the absence of a SWA return in 2 subjects, was associated with CBT phase. So perhaps when sleep occurs relative to CBT phase determines much of this variation. There would also likely be individual differences in how pronounced the 12-hour rhythm is, that may be reflected in tendencies to nap in the afternoon, or to experience a large "post-lunch dip" in performance. Measuring these variables would be an interesting addition for future research.

12-Hour Rhythm or Process S?

During the 8HBL of Study 2, when subjects were getting more sleep during the 3 days prior to extended sleep (meaning Process S should be lower, with lower pressure for SWS/SWA), ironically 2 subjects had their largest amounts of late SWS and SWA, and all subjects showed a SWA return. So it seems that increased waking prior to sleep may not increase the likelihood of late SWS or SWA increases. There was generally increased WASO during the 8HBL relative to other conditions (except Subject 2 had a similar amount during 6HBL), so perhaps the lower Process S at sleep onset allowed increased WASO that again built up Process S. As a measure of Process S, total waking (prior day + WASO) was determined, and it was found to be similar on several occasions during different conditions in the same subject, to within 7.5 minutes (e.g., Subject 1, 6HBL and EL; Subject 2, ML and EL; Subject 3, 6HBL and EL). However, these episodes with the same Process S showed quite different timing and/or magnitude of SWA maximum in the last 5 hours (Max_{Late}). This underlines the point that prior waking, in determining Process S, is only part of the story for late SWS and SWA, and that CBT phase shifts by bright light must have played some role since these shifts were the only differences between these conditions.

A SWA return was observed in one subject with virtually no WASO (only 8.5 minutes) who had a large SWA return

(Subject 7, Study 1). So these SWA returns were not simply due to longer periods of WASO building up Process S, or WASO keeping SWA reduced before a late SWA increase. It could be that the threshold of Process S that must be reached before SWA will increase is, just by coincidence, attained by most subjects after approximately 13 hours. However, as stated above, identical amounts of prior waking and WASO led to different levels of SWA occurring at different times during the extended period. So,again, there are clearly factors other than prior wakefulness that play a role in the course of SWS and SWA. Perhaps indices of brain activation other than WASO or REM (e.g., alpha or beta EEG activity) should be also considered in relation to build-up of Process S.

The idea of a 12-hour rhythm of SWS/SWA pressure that is linked to the CBT rhythm could help explain these late SWS and SWA episodes. CBT phase showed a relationship to the timing and magnitude of SWA returns and more generally to maximum levels of SWA in the last 5 hours (Max_{Late}). So it is a feasible explanation that shifting CBT also shifted a 12-hour rhythm of lowered threshold for SWS/SWA, and this could account for the differences between conditions in the same subject with the same level of Process S (i.e., same prior waking and WASO). Taken together with the evidence for an afternoon period of lowered vigilance and increased SWS during afternoon naps that disappears later in the day, the findings of Studies 1 and 2 tend to support this 12-hour rhythm. However, the delay from sleep onset to SWA return seems to be slightly greater than 12.5 hours, with a mean of 13.1 hours for all subjects in both studies who had a SWA return. But it should be noted that many of the long sleepers tended to have somewhat phase delayed CBT relative to subjects rejected for early waking and the 2 subjects with no SWA return in Study 1. This may account for the SWA returns occurring later than the predicted 12.5 hours.

It is possible that effects of bright light, independent of CBT, may have played a role in the SWS and SWA findings. However, since similar CBT phase to SWS and SWA relationships appeared to exist for Study 1, which had no systematic use of bright light, as well as Study 2, this seems not likely.

2-Oscillator Model

These results support the notion that there is a relationship between the CBT rhythm and SWS or SWA, which are supposed to be controlled by separate oscillators (X and Y respectively), according to the 2-Oscillator Model (Kronauer et al., 1982). SWS and SWA showed high levels near sleep onset and also a late increase, supporting the need for the Y oscillator to account for this (perhaps by the split to Y1 and Y2). The finding that CBT phase was related to timing of the late SWA pulse may indicate that the two oscillators have a stable phase relationship. The results of Study 2, that CBT phase shifts by bright light are associated with timing of Max_{Late} SWA (in 2 of 3 subjects), could be interpreted to mean that both oscillators may be influenced by bright light, or that the coupling from X to Y is quite strong.

Conclusions

In summary, the following account can be drawn from the above information. The 2-Process Model is not supported in that WASO had a non-significant (but positive) association with levels of SWS and SWA late in the sleep period, or when this SWA will occur. On the other hand, CBT phase was related to the magnitude and timing of this SWS and SWA late in sleep. This supports the notion that there is a 12-hour rhythm of lowered threshold for SWS/SWA (Broughton, 1975; 1988), that is linked to the phase of CBT rhythm. The phase of CBT is thus important to the timing and magnitude of the minor pole of this 12-hour rhythm, but Process S, which has

much support elsewhere, is likely associated with the magnitude of SWA expressed at the both major and minor SWS/SWA poles. It may be that under the special conditions of extended sleep, a link between Process S and SWA was not seen. This relationship between CBT phase and SWS/SWA windows are likely reflected in the phase shifts of the SWS return seen in Gagnon et al. (1985) that were accomplished by sleep timing.

Future Research

At this point, the link between CBT and a 12-hour rhythm of SWS/SWA is just an association. Larger samples of subjects in variations of Study 2, where CBT phase was manipulated, could establish if a causal relationship exists. Since it has previously been shown that SWS correlated strongly with tympanic temperature but not with rectal temperature (Berger and Phillips, 1988; Morairty et al., 1988), another important variable to measure would be brain temperature, to determine whether SWS and SWA do indeed serve a thermoregulatory function for the brain (supported by Szymusiak and McGinty, 1990), during the SWS/SWA return that is simply not reflected in rectal CBT which may take longer to change. Also, some form of constant routine would give a better indication of CBT phase. A constant routine could perhaps directly follow wake-up after the 15 hour sleep period, or conversely, the extended sleep could follow a constant routine of fixed amount (although the effects of sleep deprivation may disrupt the time course of SWA in the subsequent sleep). Perhaps other circadian markers (e.g. cortisol, melatonin) would give valuable additional information about how SWS and SWA may be linked to circadian processes.

Another possibility for future research would be to follow the same procedure as Study 2, but with sleep onset at the minor pole (12:00h to 13:00h), so that the SWS or SWA

"return" would actually be during the major pole of the postulated 12-hour rhythm. This may enhance the chances of larger SWS and SWA episodes near the end of an extended sleep, so that there would be more data with which to compare the effects of CBT phase shifts and other manipulations. Perhaps a constant routine could directly precede this extended sleep period, to get unmasked circadian markers, and to standardize the amount of prior waking.

It would be interesting to monitor if subjects with prominent SWA returns also exhibit napping tendencies and/or large declines in performance at that same time of day. If this 12-hour rhythm strongly relates to fluctuations in vigilance and performance, and it can be indexed by CBT phase, and be phase shifted by bright light, there would be many practical applications for shift work (e.g. a way to know if a worker is at increased risk of errors, and be able to shift this zone where it would be less dangerous), or readjusting to new time zones.

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Appendix 1

MMPI scores for subjects in Study 1 and Study 2.

Appendix 1

MMPI scores for subjects in Study 1 and Study 2.

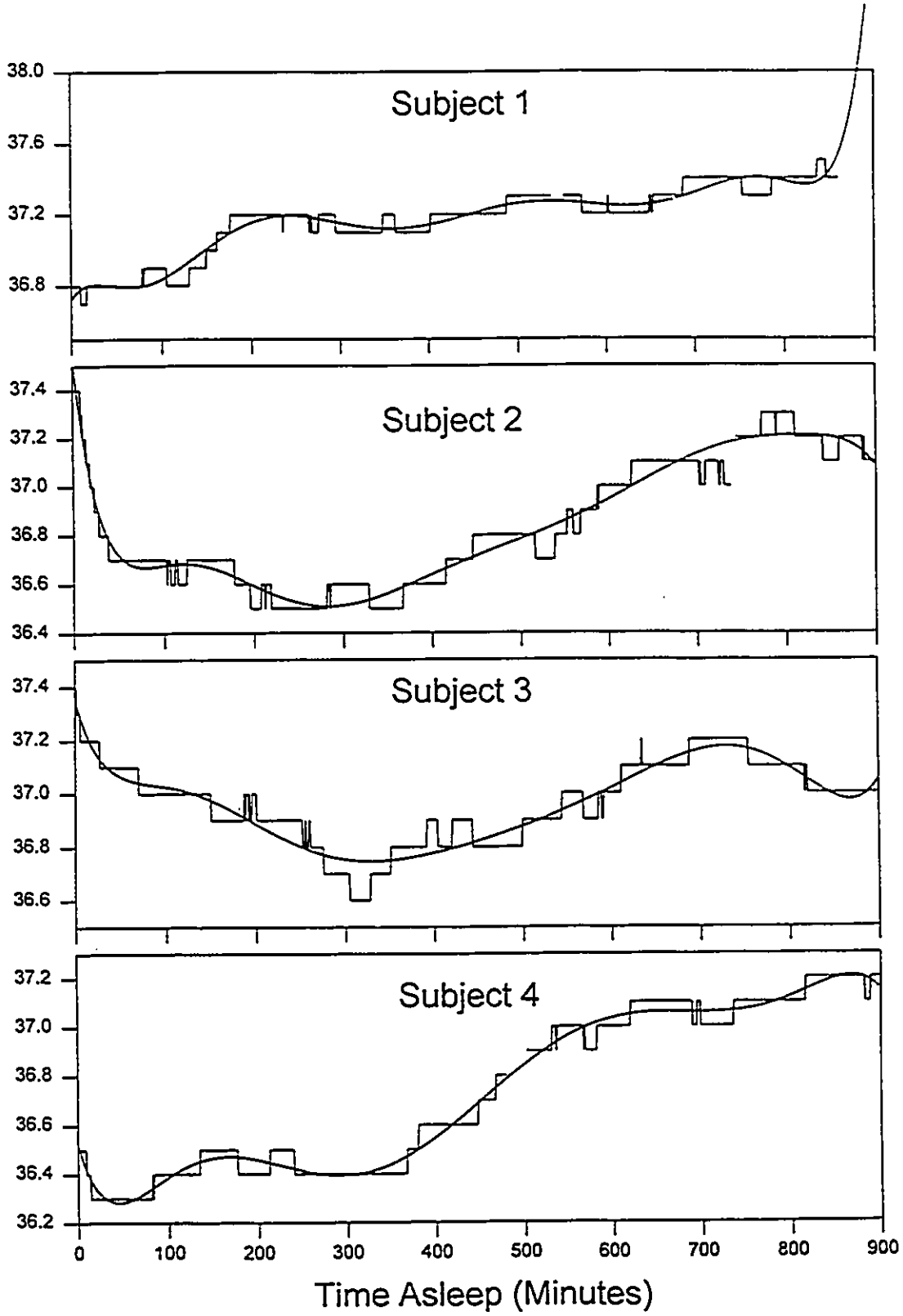
	MMPI Scale											
Subject	L	F	K	Hs+.5K	D	Hy	Pd+.4K	Mf	Pa	Pt+1K	Sc+1K	Ma+.2K	Si
Study 1													
1	6	8	11	14	30	27	19	39	8	15	18	12	15
2	3	6	16	11	22	20	19	33	15	31	31	16	25
3	3	6	7	6	16	15	13	36	11	25	22	22	29
4	6	1	15	10	19	21	23	39	7	18	22	20	20
5	5	4	12	9	20	15	17	35	2	31	30	22	24
6	3	6	15	18	22	23	22	29	9	29	26	22	16
7	4	11	13	21	32	30	27	36	11	35	38	24	38
Study 2													
1	2	2	19	11	16	18	20	23	10	24	24	24	11
2	2	5	13	12	12	20	24	28	11	26	30	25	14
3	3	2	14	10	13	15	21	31	9	23	28	24	13

Appendix 2

Ninth degree polynomials fitted to core body temperature curves

Study 1 is shown first, followed by Study 2, with one subject per page. CBT is in degrees Celsius.

Study 1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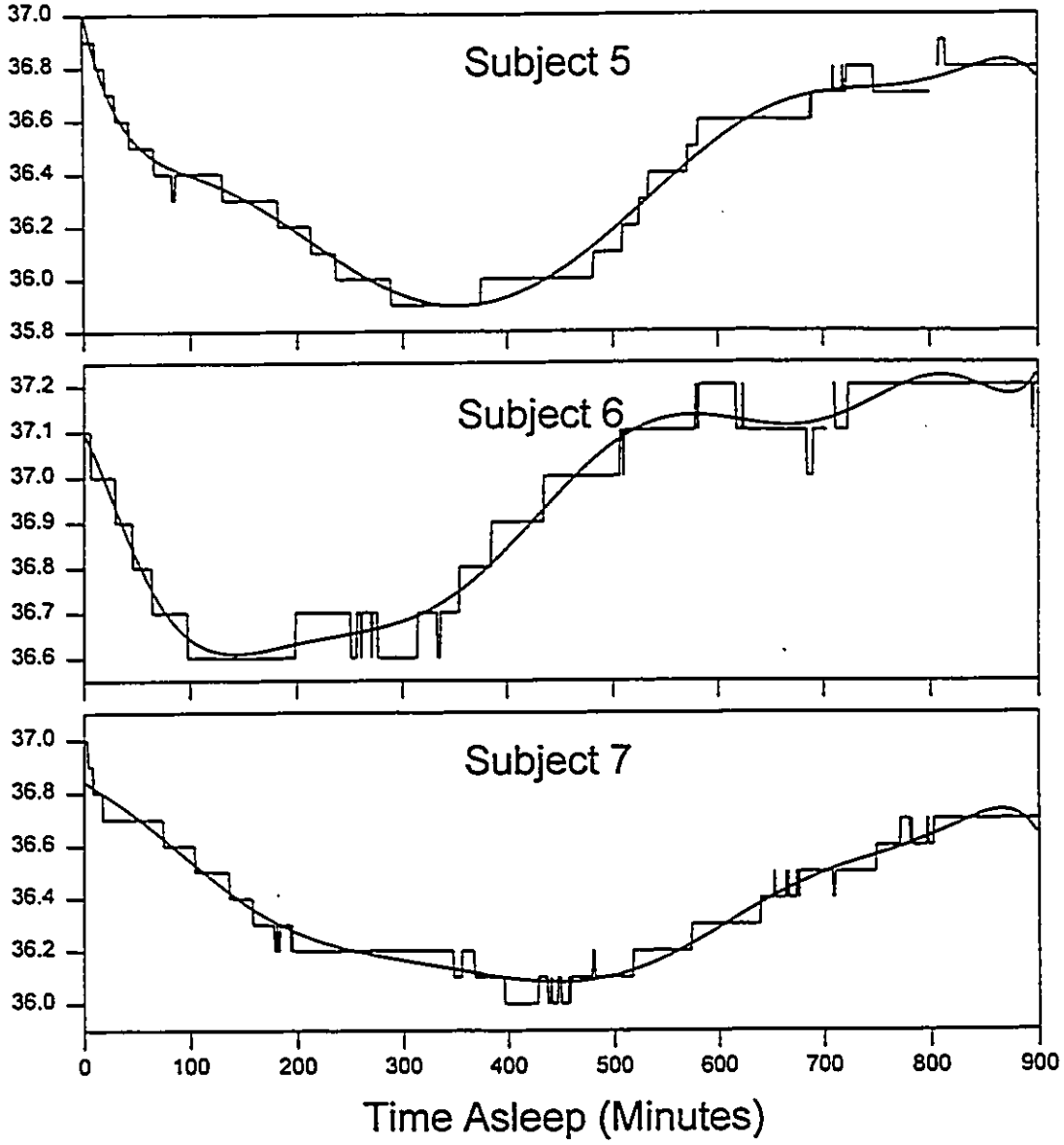
37.2
36.8
Subject 2
37.4
37.2
37.0
36.8
36.6
36.4
Subject 3
37.4
37.2
37.0
36.8
36.6
Subject 4
37.2
37.0
36.8
36.6
36.4
36.2
0
100
200
300
400
500
600
700
800
900
Time Asleep (Minutes)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Subject 6
Subject 7
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37.1
37.0
36.9
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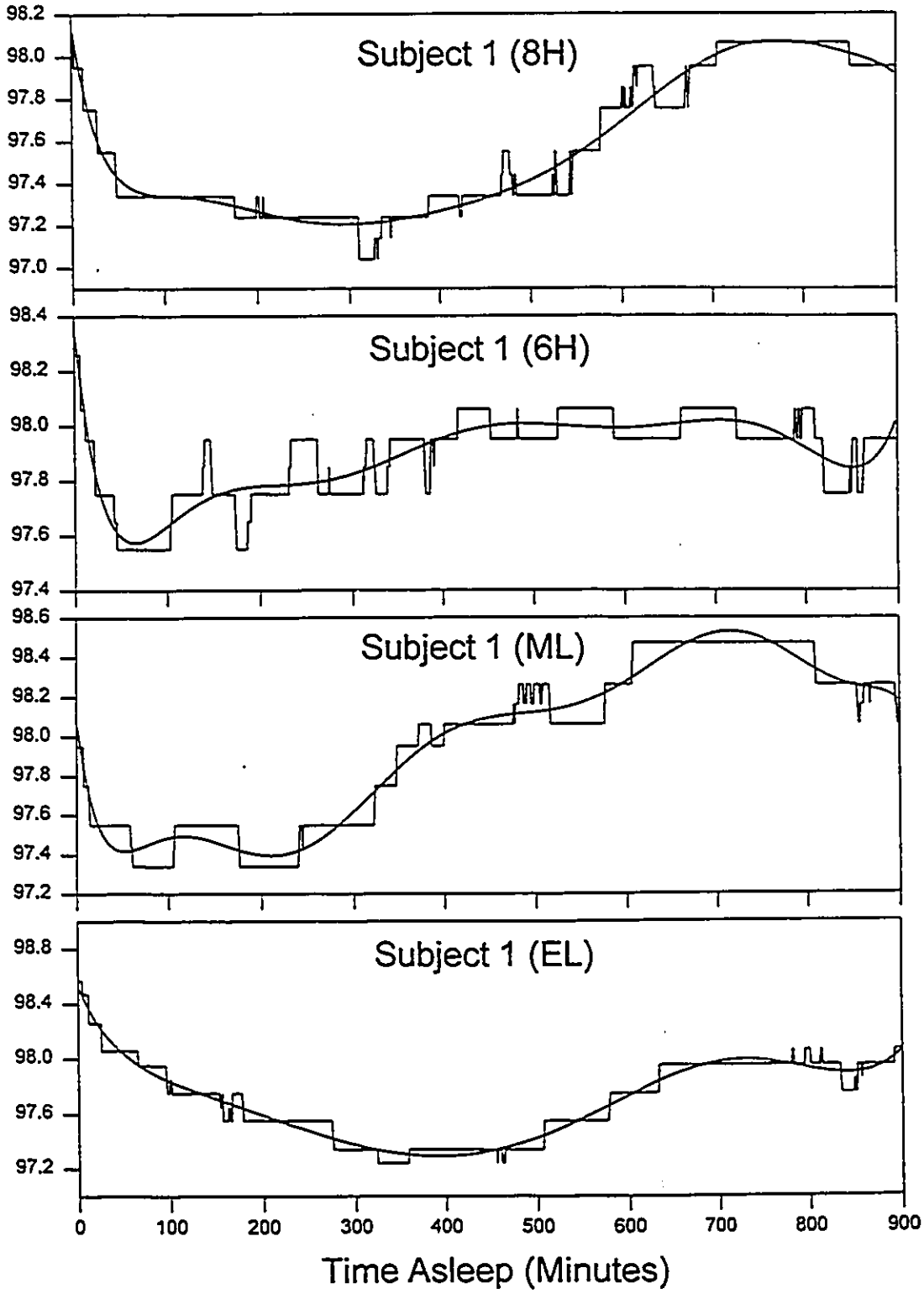
36.7
36.6
0
100
200
300
400
500
600
700
800
900
Time Asleep (Minutes)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98.0
97.8
97.6
97.4
97.2
97.0
Subject 1 (6H)
98.4
98.2
98.0
97.8
97.6
97.4
Subject 1 (ML)
98.6
98.4
98.2
98.0
97.8
97.6
97.4
97.2
Subject 1 (EL)
98.8
98.4
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97.6
97.2
0
100
200
300
400
500
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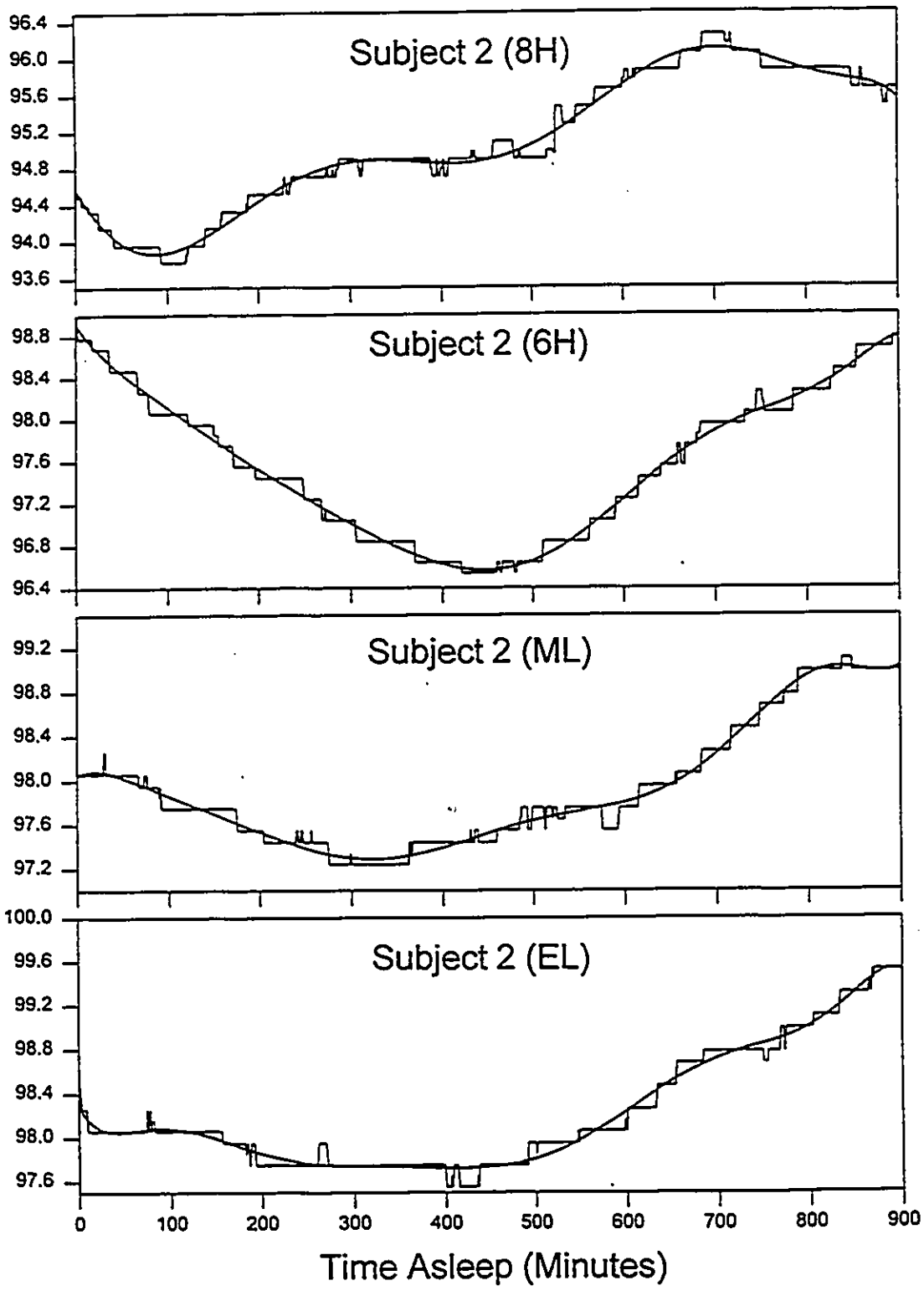
700
800
900
Time Asleep (Minutes)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95.2
94.8
94.4
94.0
93.6
Subject 2 (6H)
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98.4
98.0
97.6
97.2
96.8
96.4
Subject 2 (ML)
99.2
98.8
98.4
98.0
97.6
97.2
Subject 2 (EL)
100.0
99.6
99.2
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98.0
97.6
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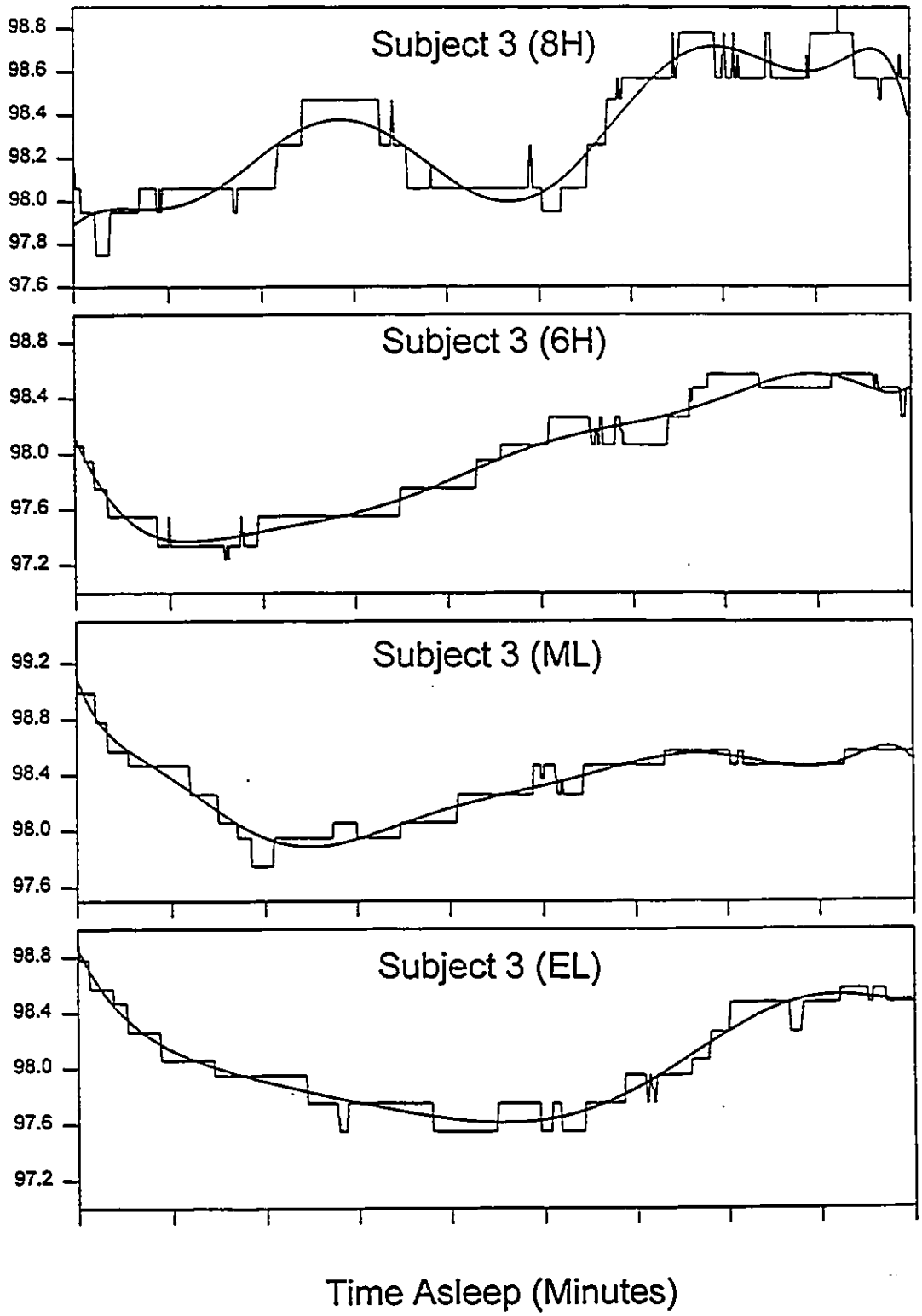
Time Asleep (Minutes)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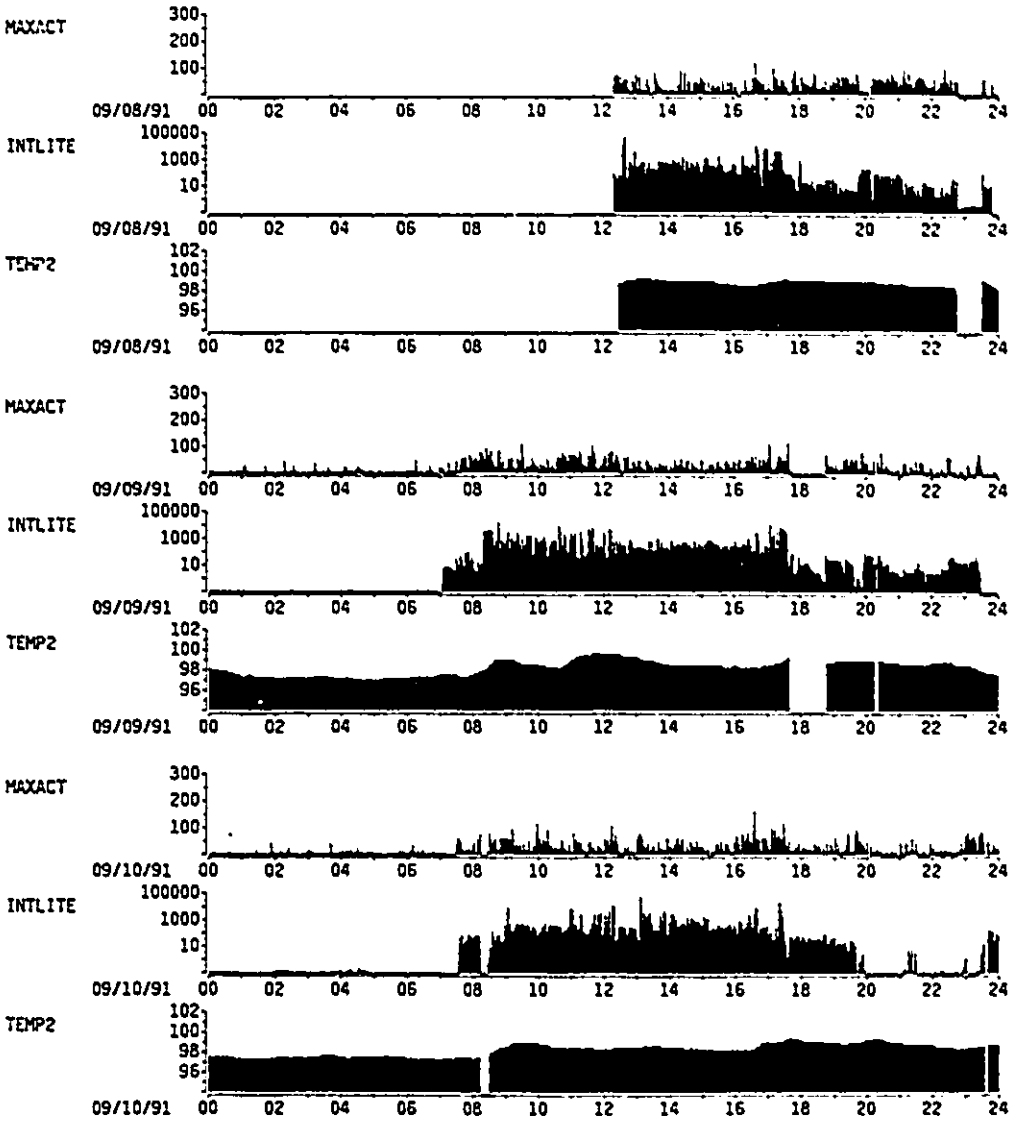
98.0
97.8
97.6
Subject 3 (6H)
98.8
98.4
98.0
97.6
97.2
Subject 3 (ML)
99.2
98.8
98.4
98.0
97.6
Subject 3 (EL)
98.8
98.4
98.0
97.6
97.2
Time Asleep (Minutes)

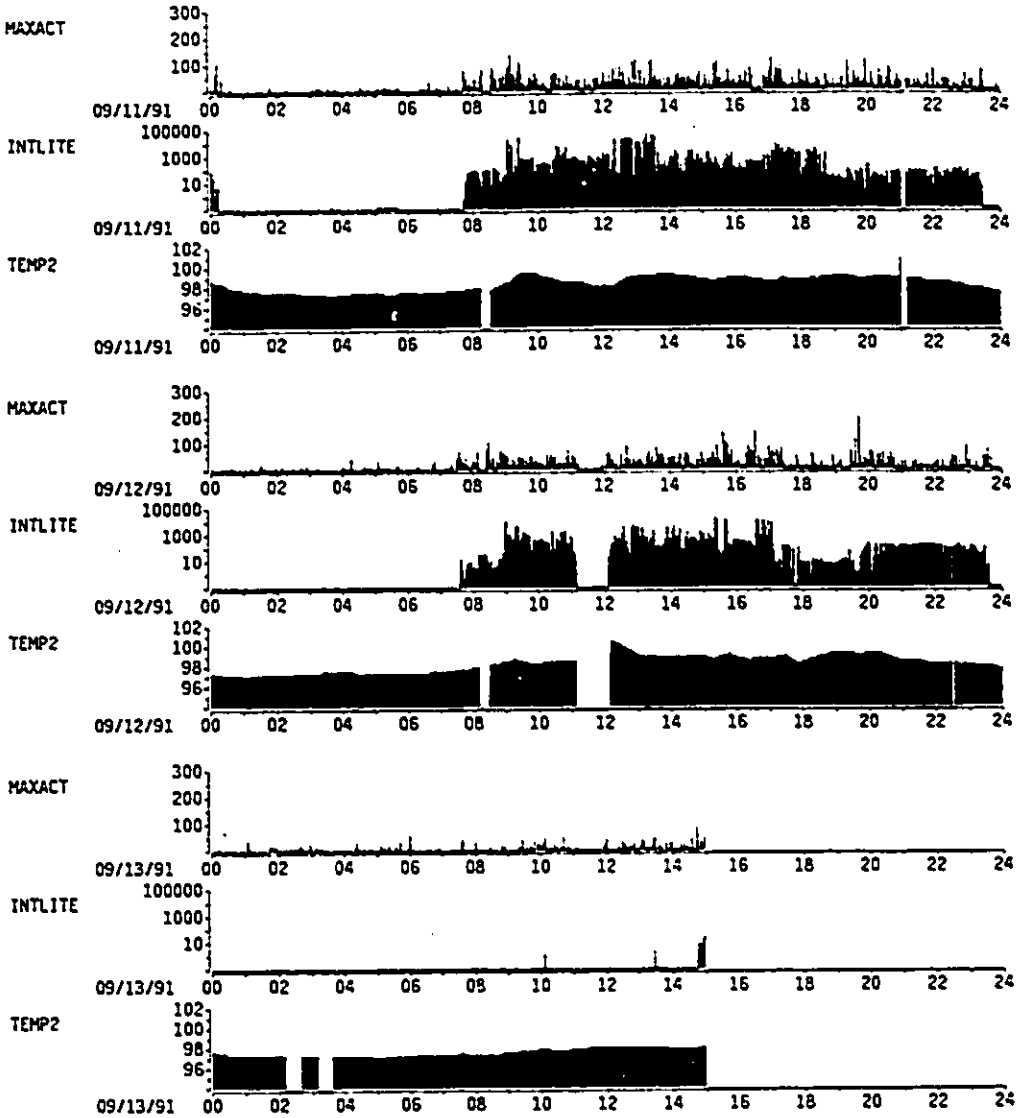
Appendix 3

Actillume records from Study 2

Activity is given by "Maxact."
Light exposure is given by "Intlite."
Core body temperature is given by "Temp" or "Temp2."

Actillume data: Subject 1, SHBL

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200
100
09/11/91
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
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TEMP2
102
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98
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09/11/91
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
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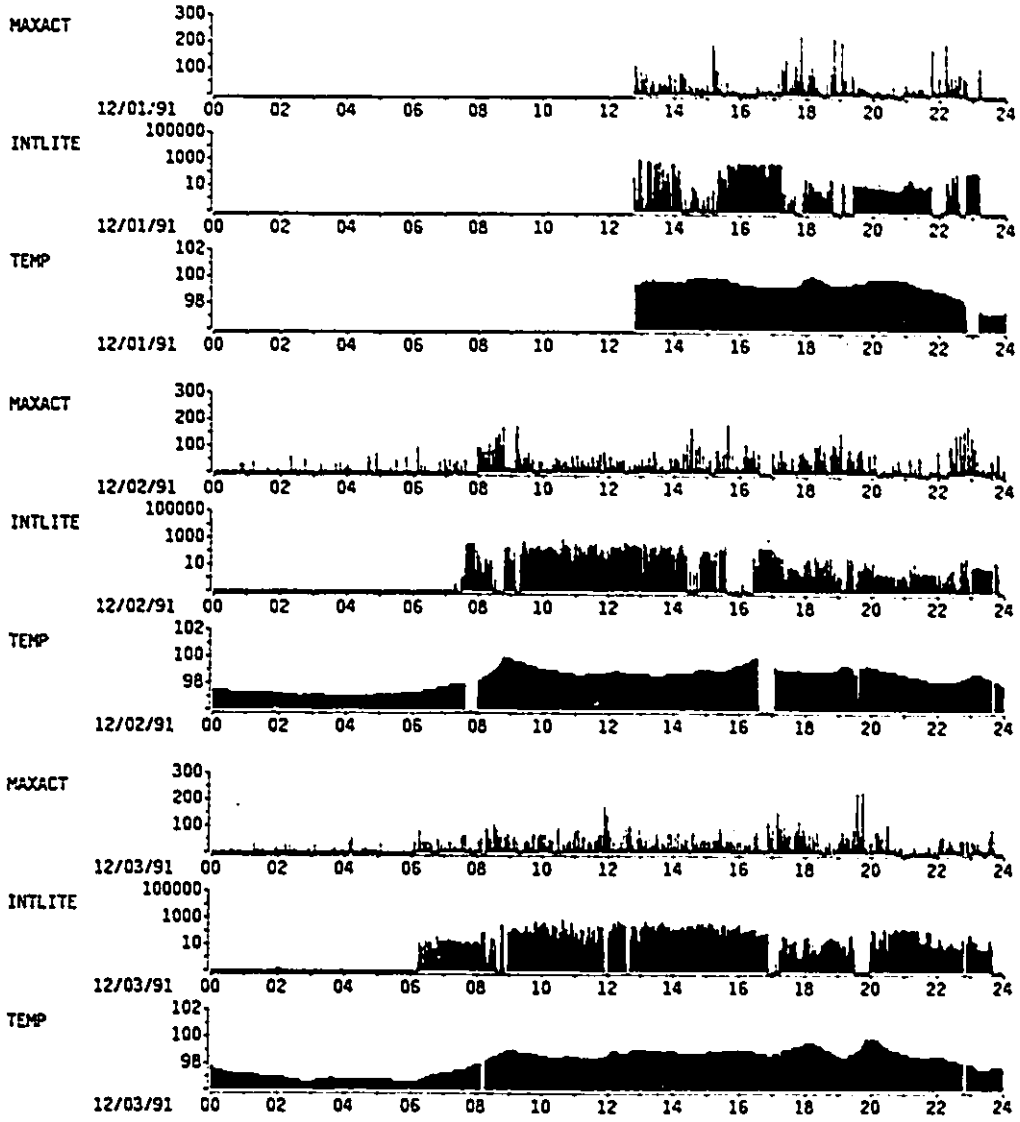
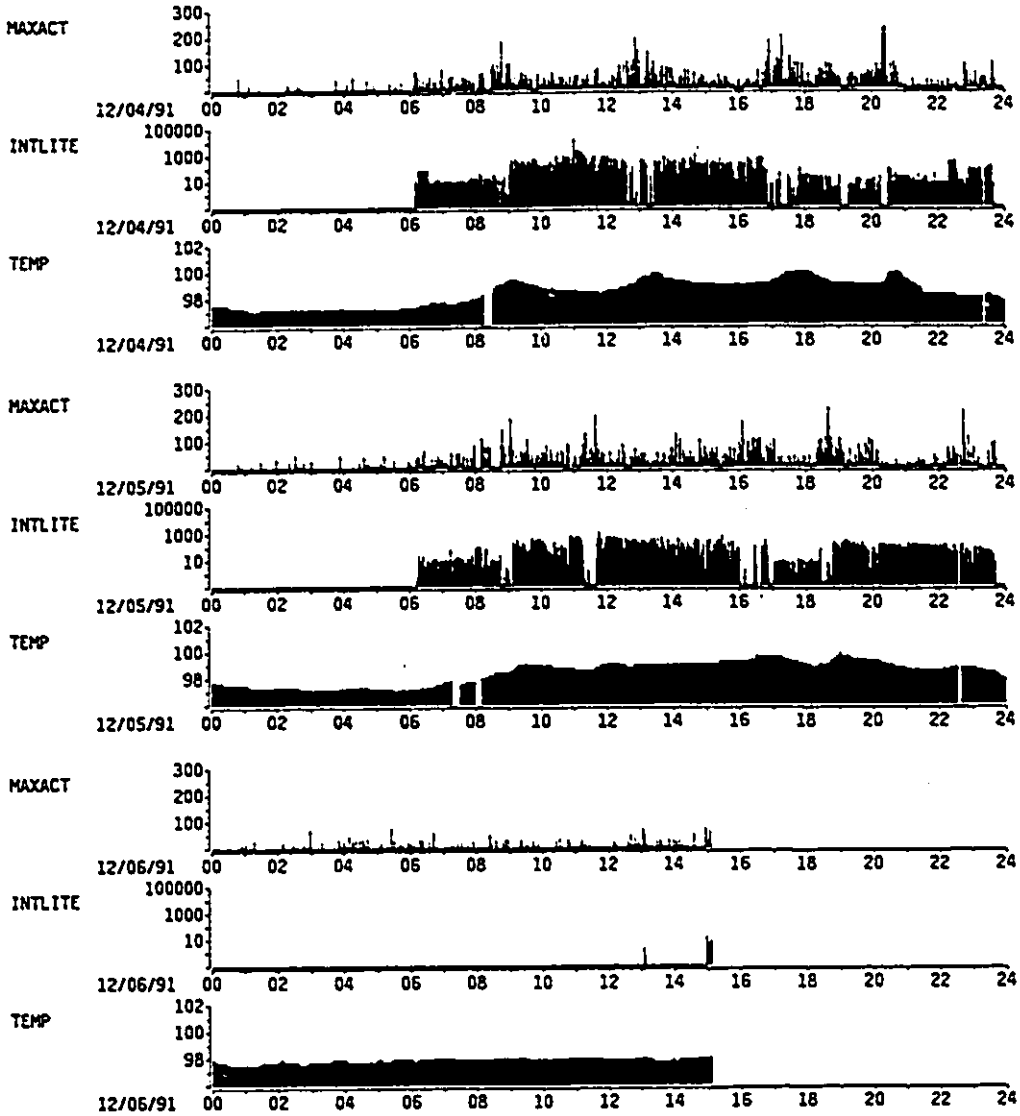
Actillume data: Subject 1, 6HBL

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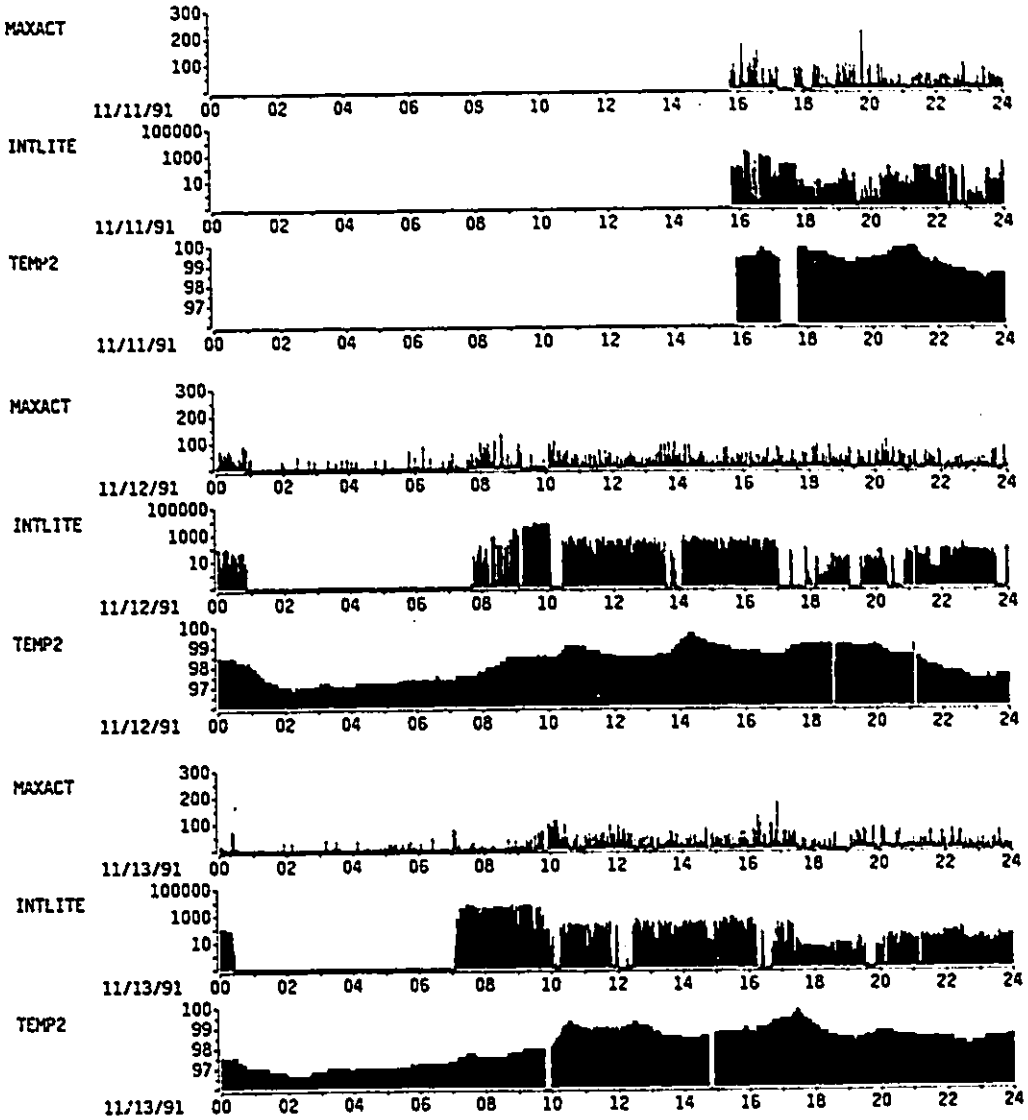
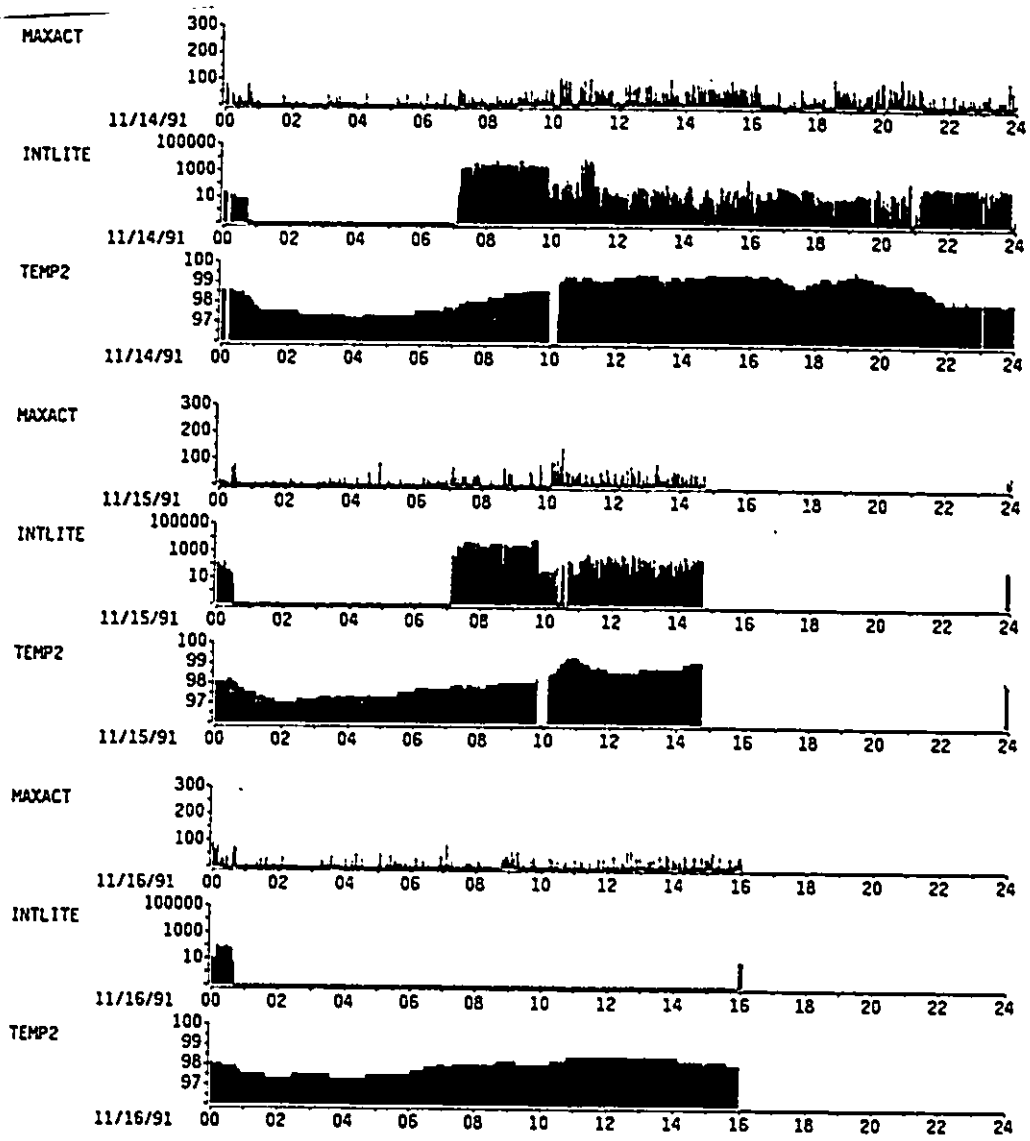
Actillume data: Subject 1, ML

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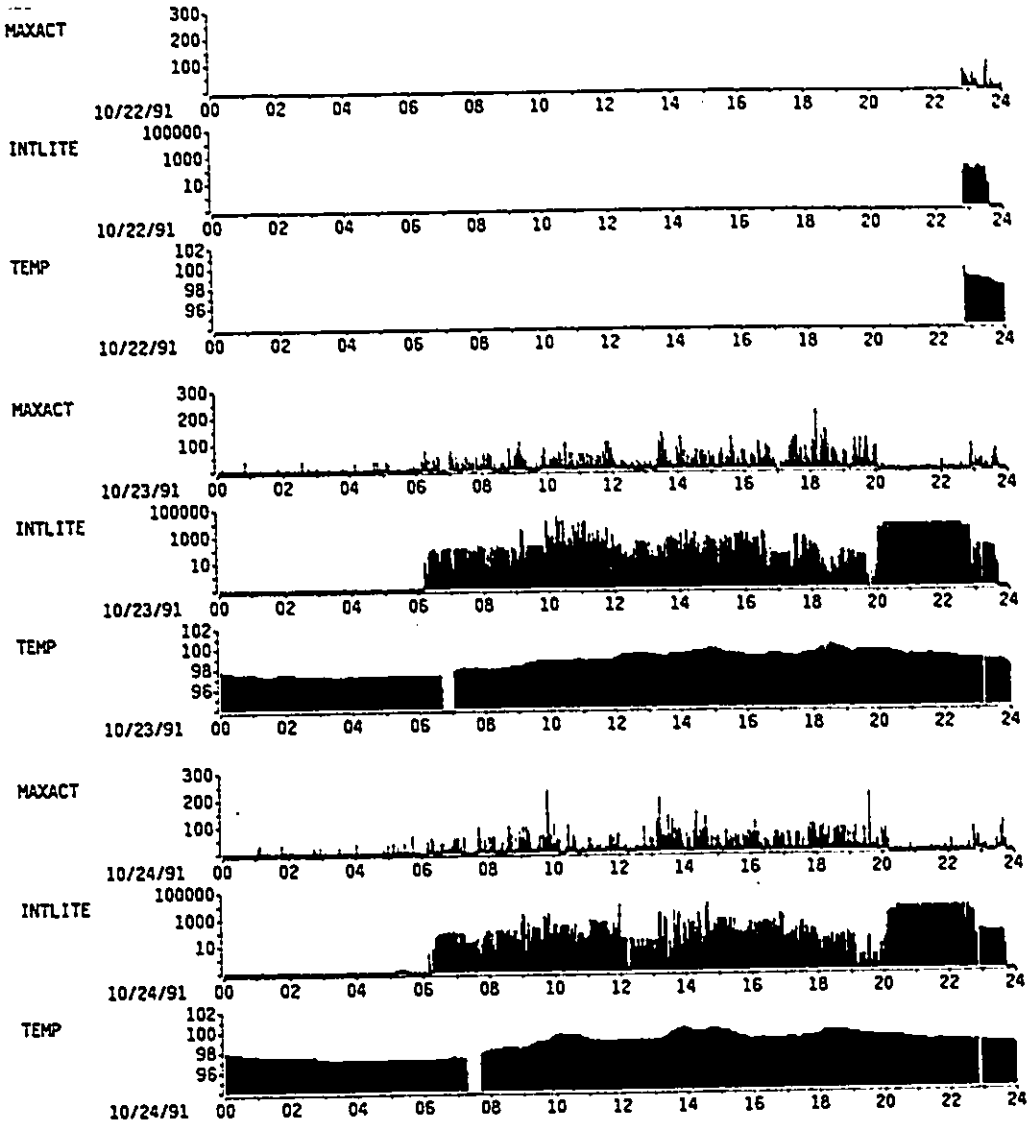
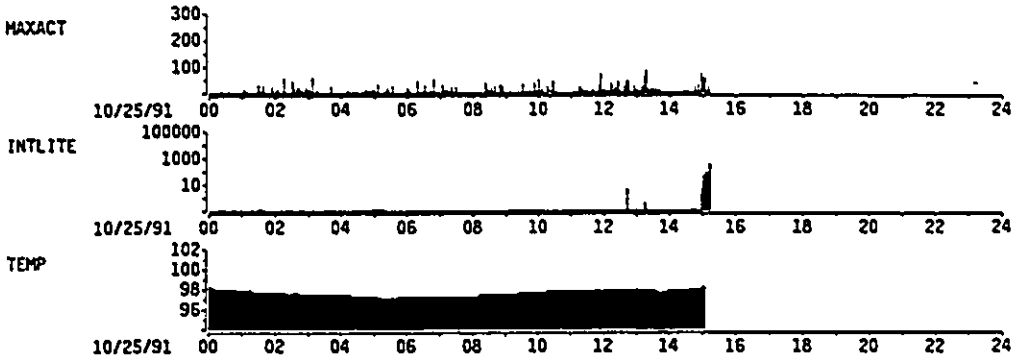
Actillume data: Subject 1, EL

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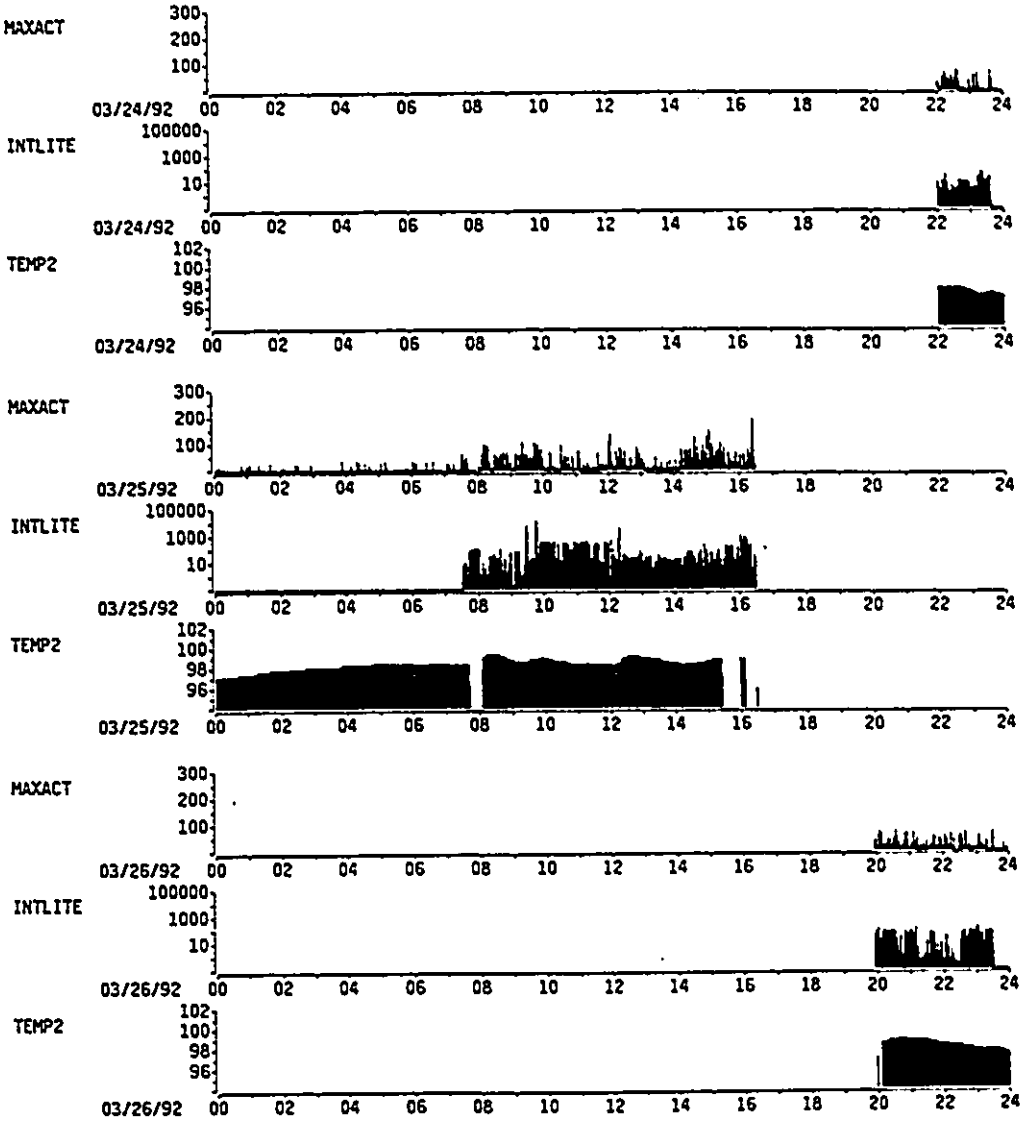
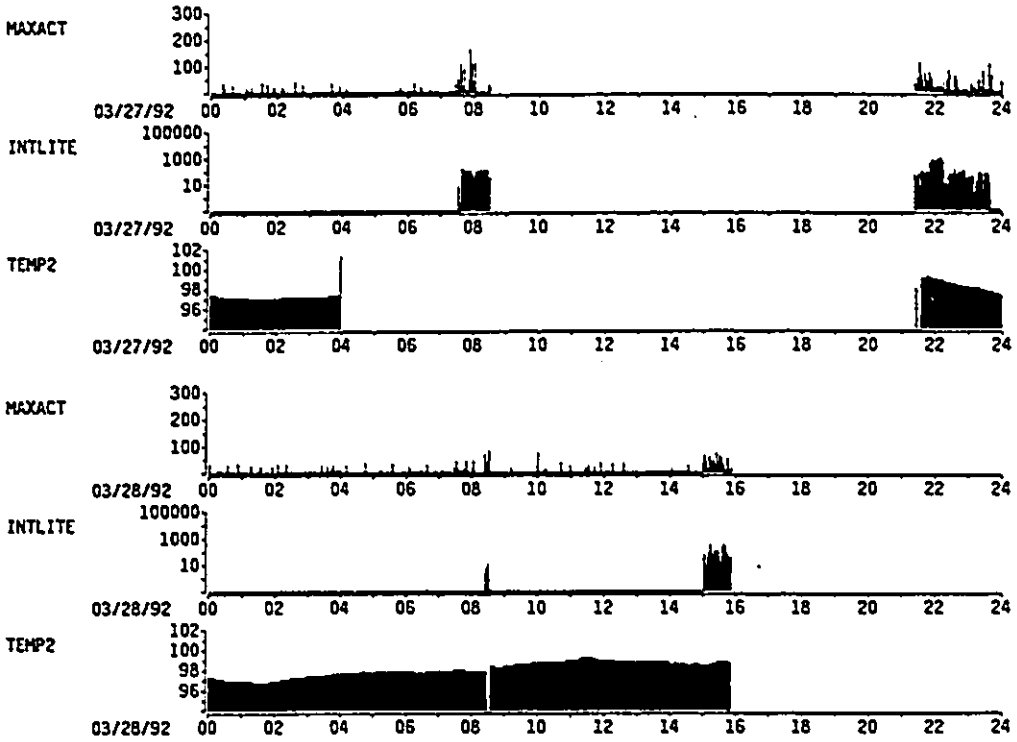
00 02 04 06 08 10 12 14 16 18 20 22 24

Actillume data: Subject 2, 8HBL

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200
100
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP2
102
100
98
96
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
300
200
100
03/28/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
03/28/92
00 02 04 06 08 10 12 14 16 18 20 22 24
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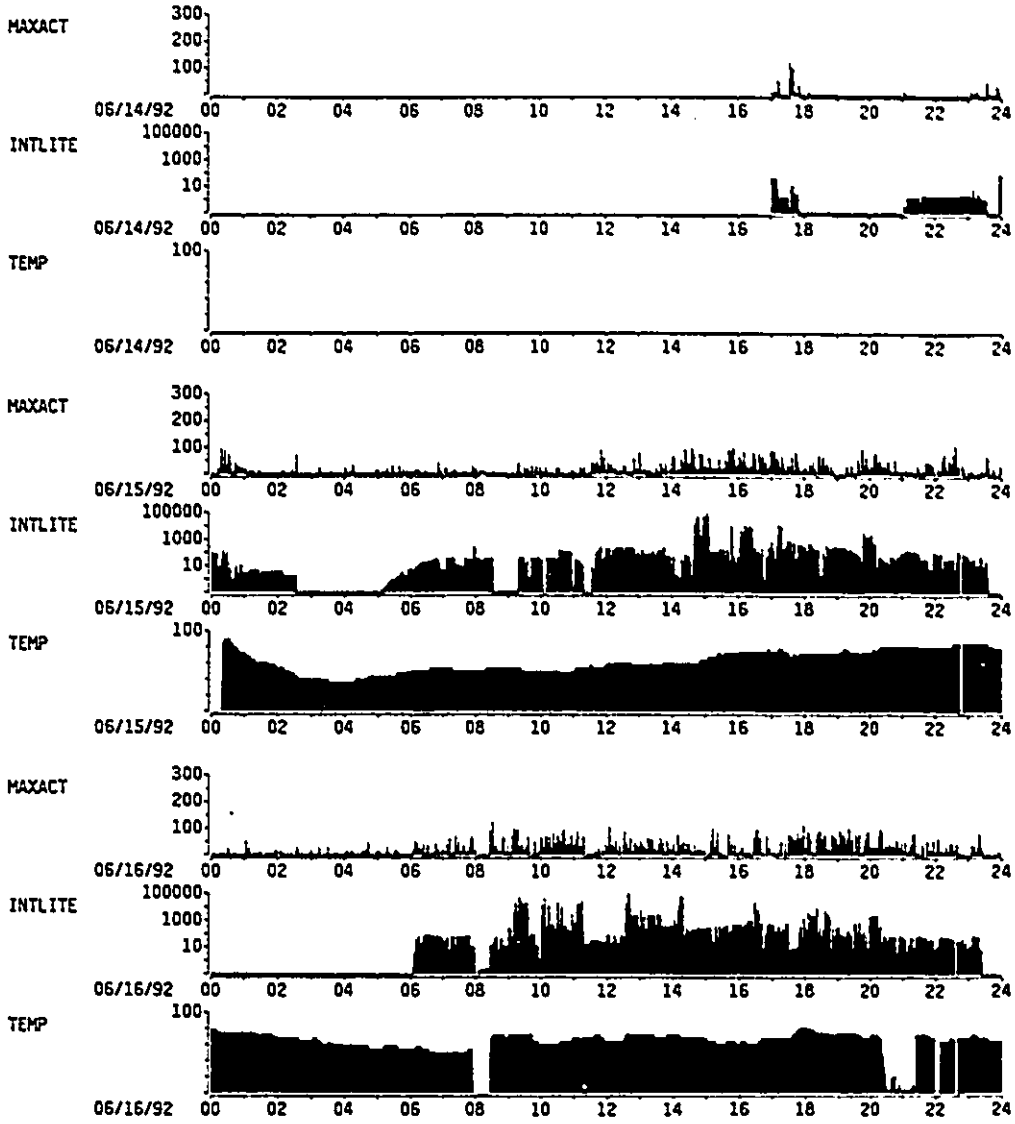
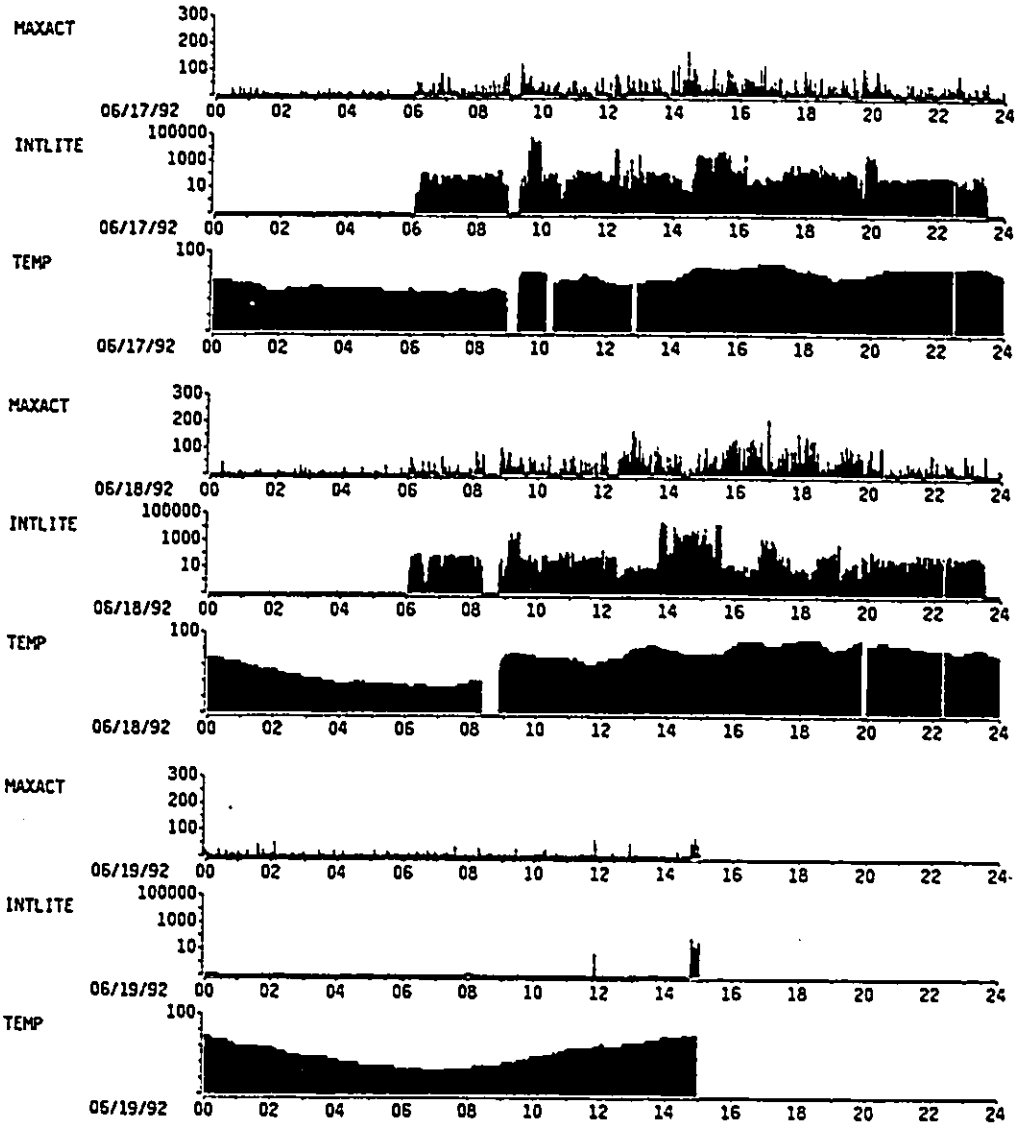
98
96
03/28/92
00 02 04 06 08 10 12 14 16 18 20 22 24

Actillume data: Subject 2, 6HBL

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06/17/92
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INTLITE
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1000
10
06/17/92
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TEMP
100
06/17/92
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MAXACT
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200
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06/18/92
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TEMP
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200
100
06/19/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
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1000
10
06/19/92
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TEMP
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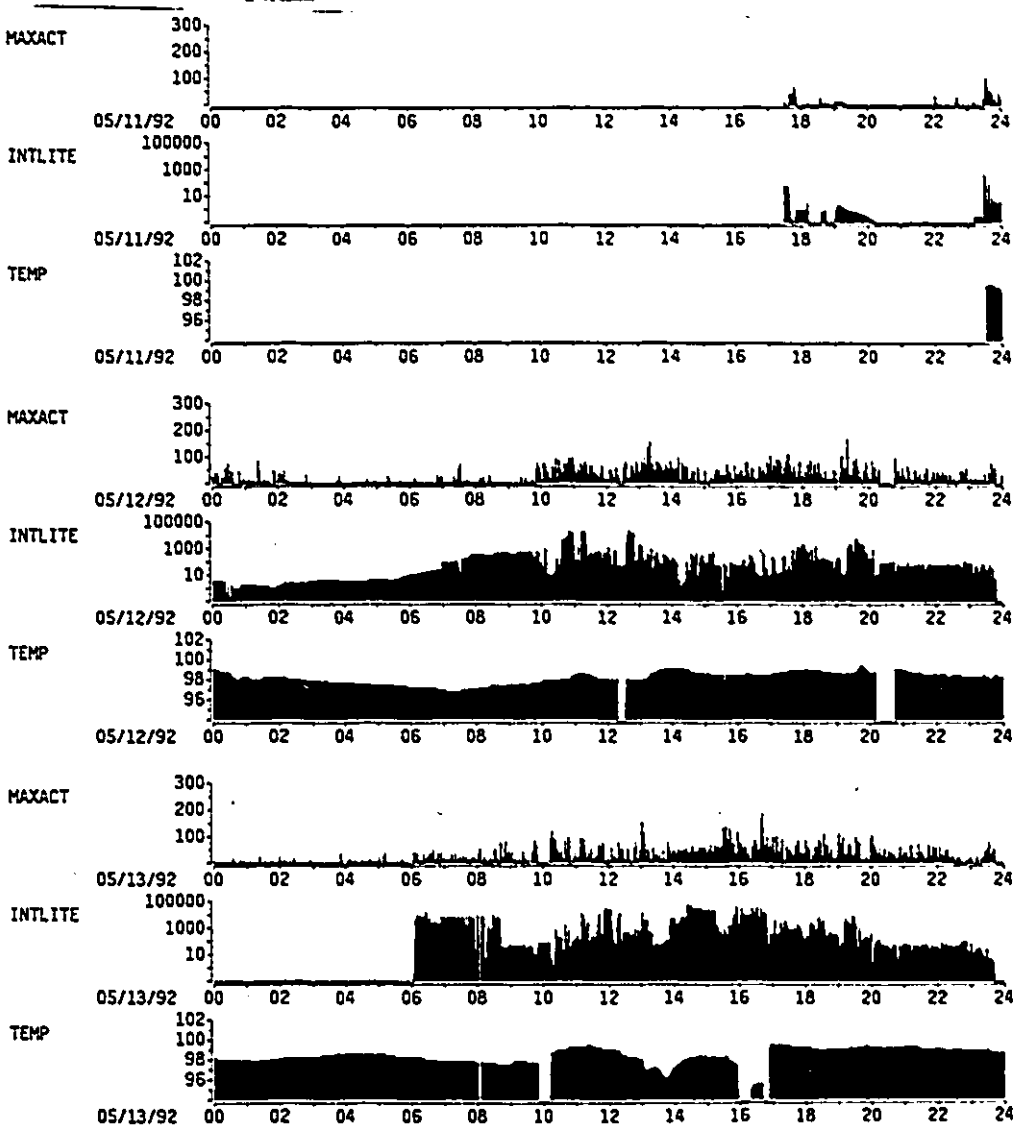
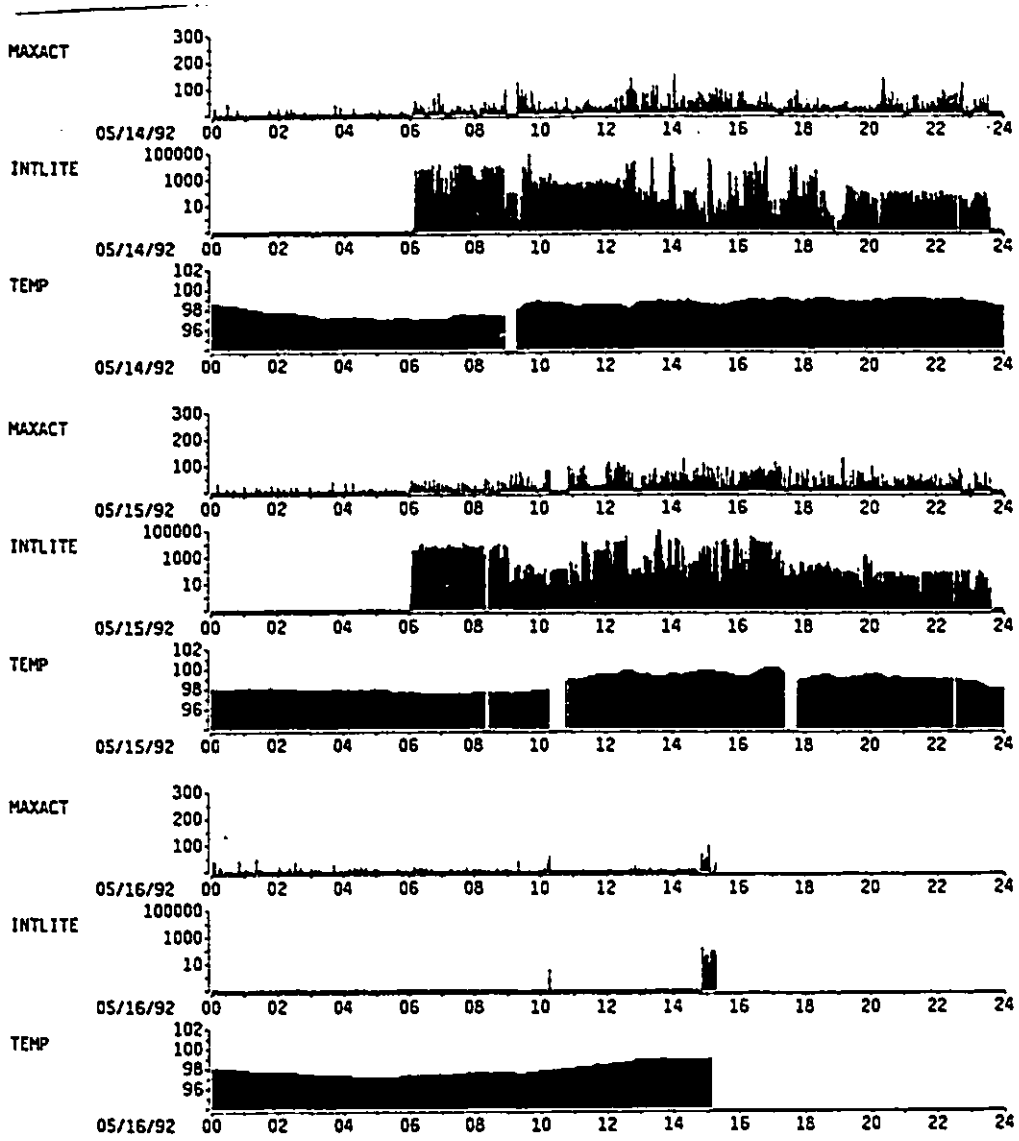
06/19/92
00 02 04 06 08 10 12 14 16 18 20 22 24

Actillume data: Subject 2, ML

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05/14/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
05/14/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP
102
100
98
96
05/14/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
300
200
100
05/15/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
05/15/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP
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100
98
96
05/15/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
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200
100
05/16/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
05/16/92
00 02 04 06 08 10 12 14 16 18 20 22 24
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100
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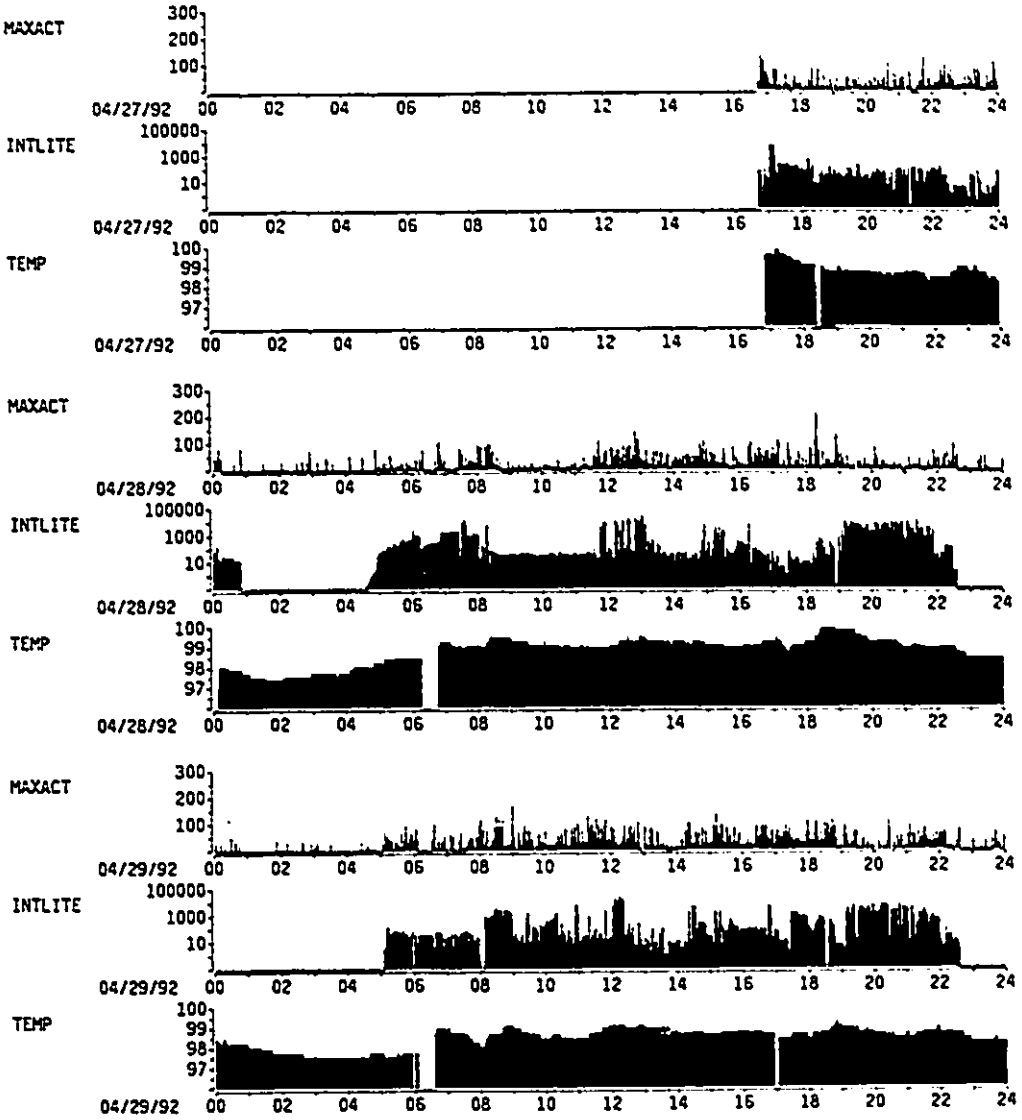
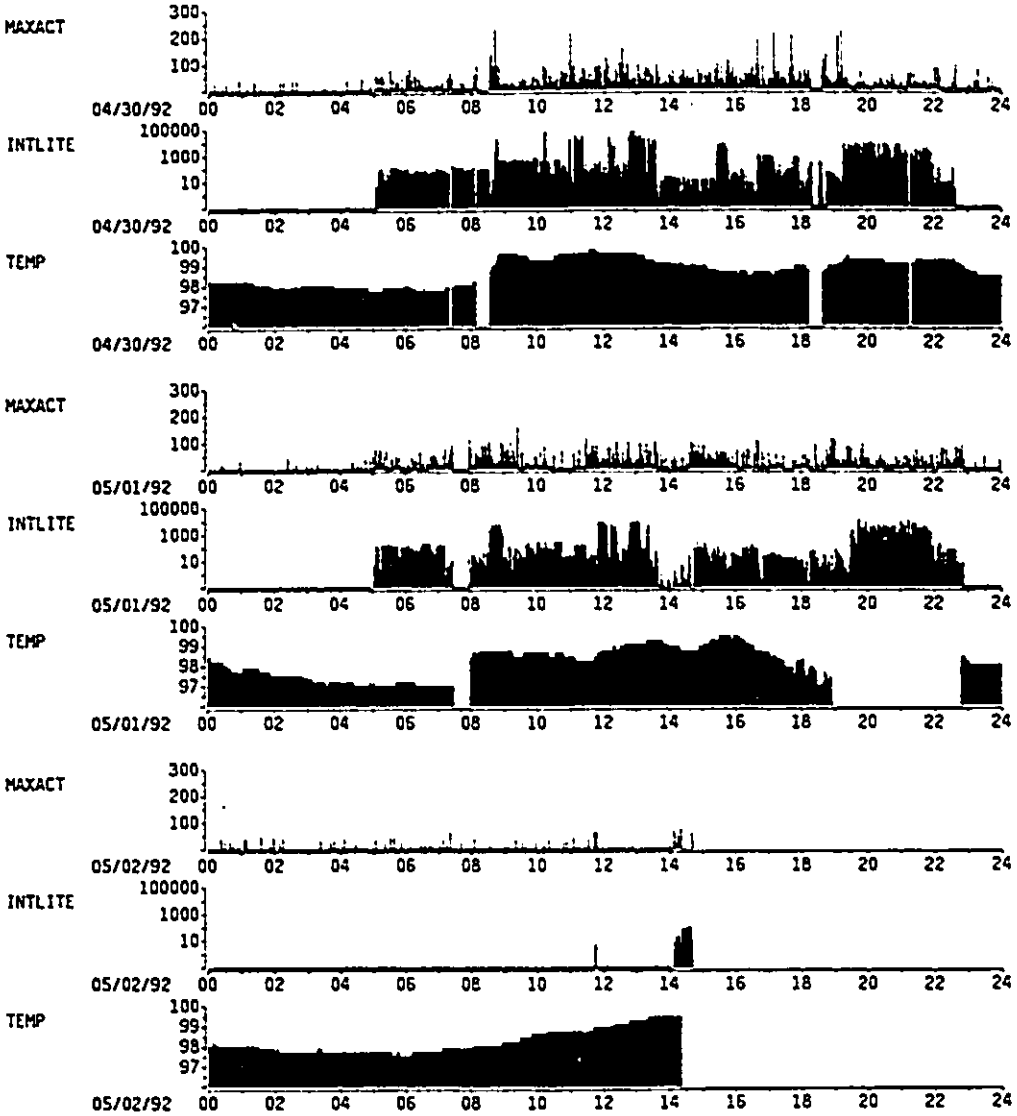
05/16/92
00 02 04 06 08 10 12 14 16 18 20 22 24

Actillume data: Subject 2, EL

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04/30/92
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INTLITE
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1000
10
04/30/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP
100
99
98
97
04/30/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
300
200
100
05/01/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
05/01/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP
100
99
98
97
05/01/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
300
200
100
05/02/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
05/02/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP
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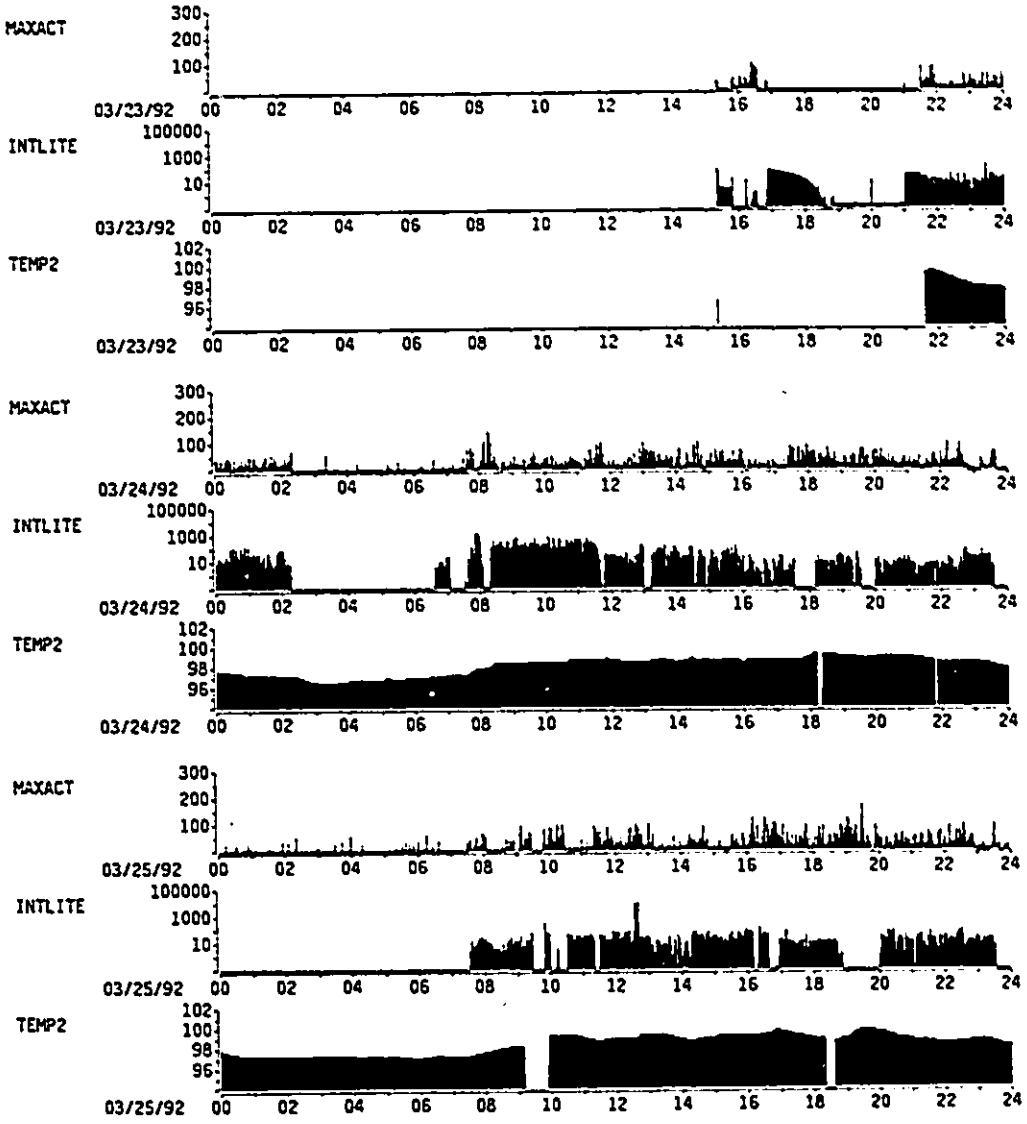
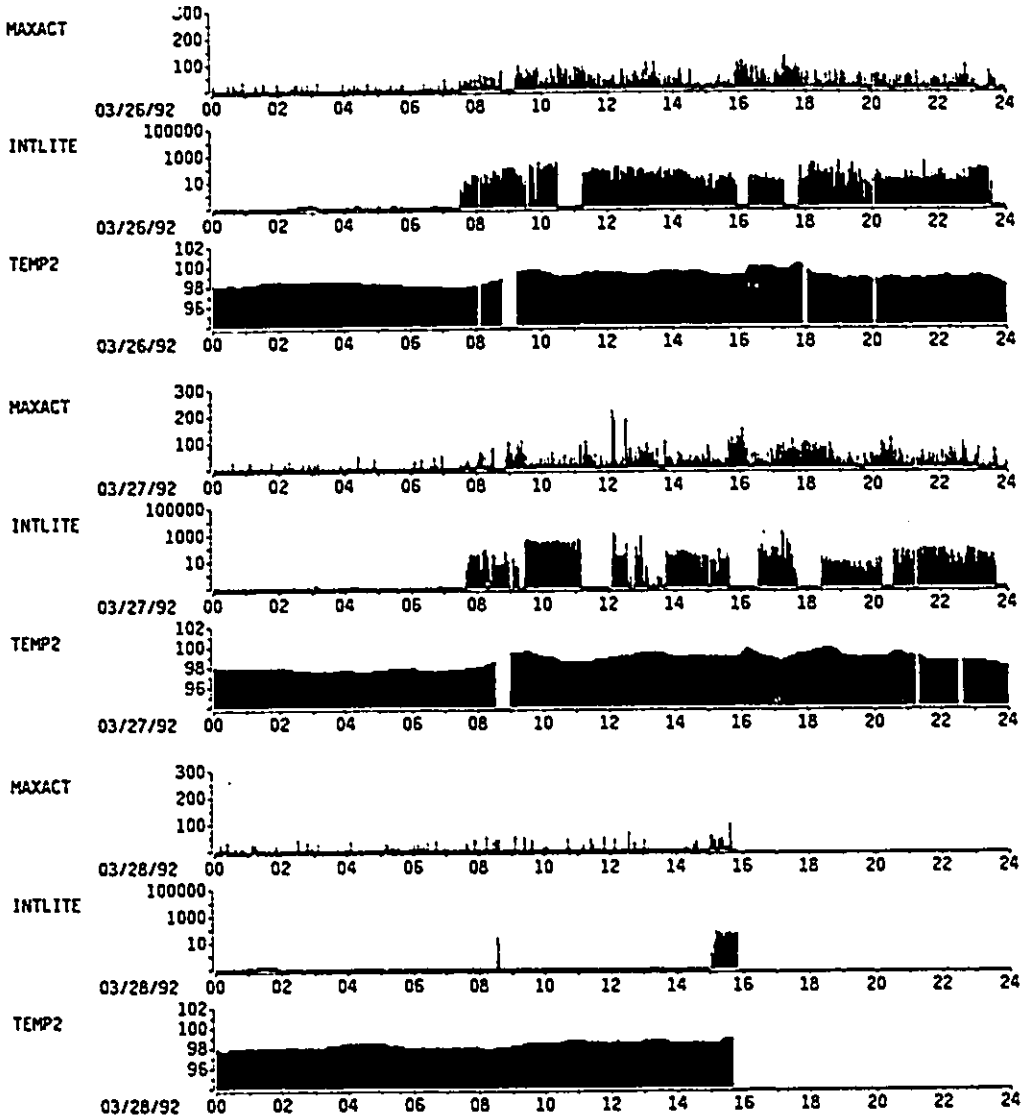
99
98
97
05/02/92
00 02 04 06 08 10 12 14 16 18 20 22 24

Actillume data: Subject 3, SHSL

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INTLITE
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1000
10
03/26/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP2
102
100
98
96
03/26/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
300
200
100
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
TEMP2
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100
98
96
03/27/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
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200
100
03/28/92
00 02 04 06 08 10 12 14 16 18 20 22 24
INTLITE
100000
1000
10
03/28/92
00 02 04 06 08 10 12 14 16 18 20 22 24
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98
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03/28/92
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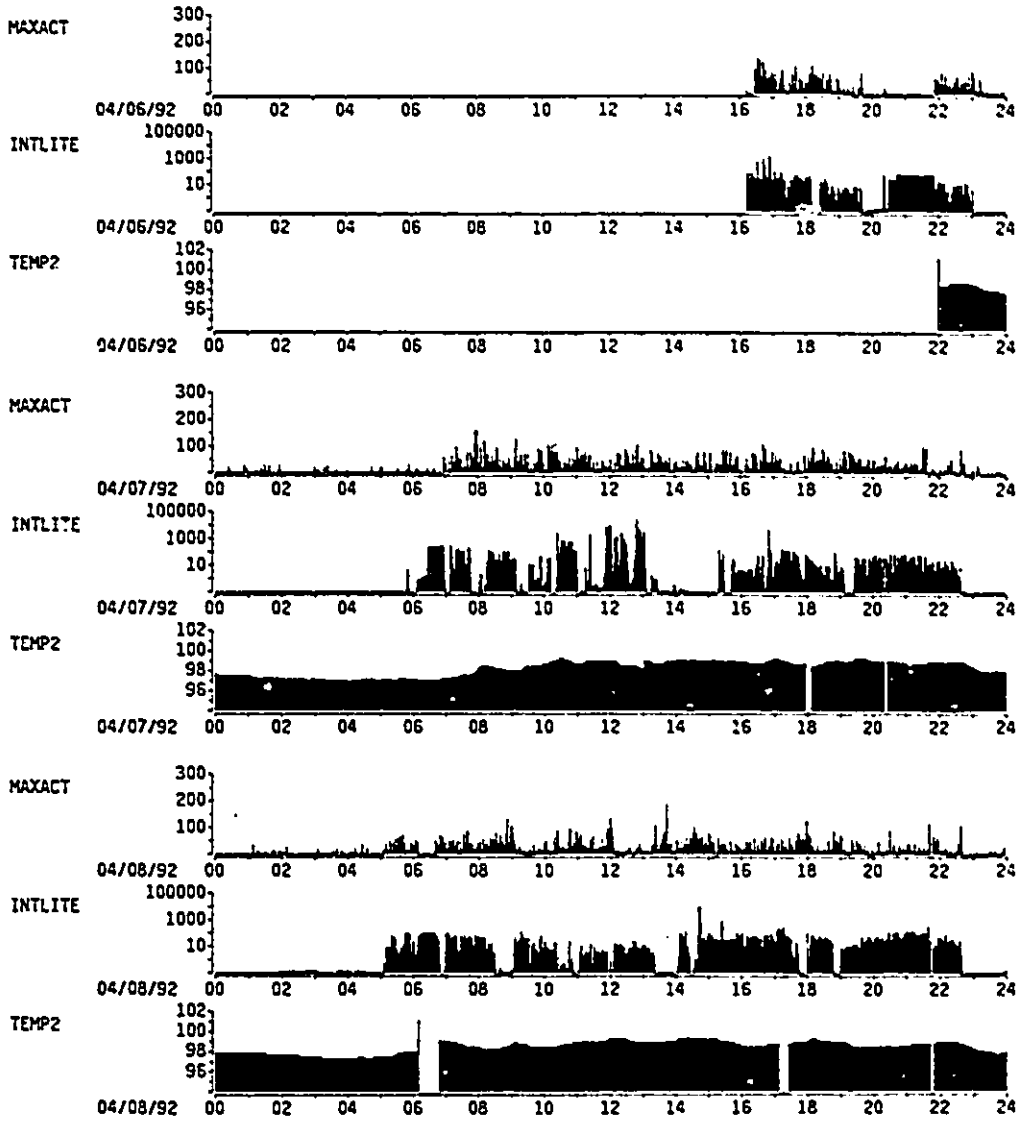
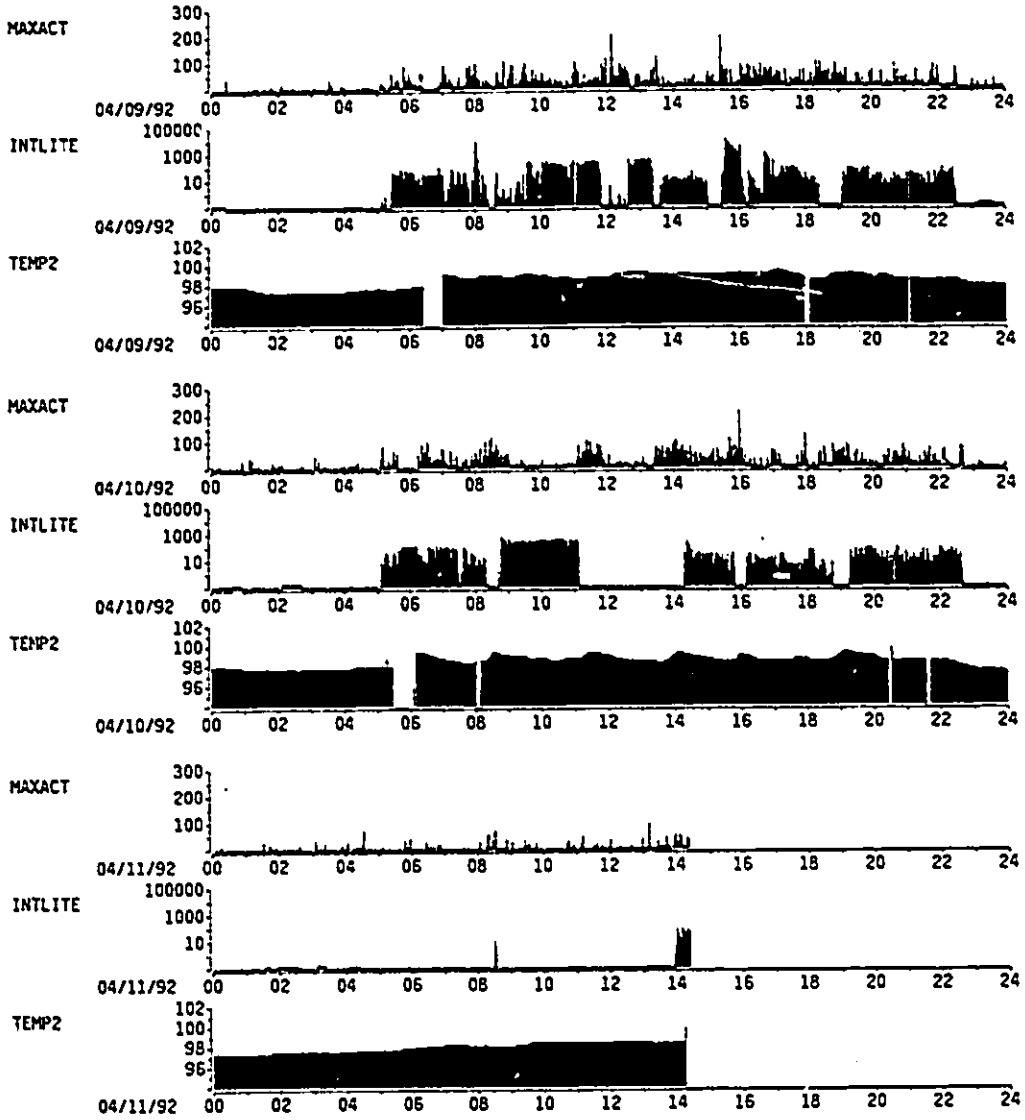
Actillume data: Subject 3, 6HBL

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10
04/09/92
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TEMP2
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100
98
96
04/09/92
00 02 04 06 08 10 12 14 16 18 20 22 24
MAXACT
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04/10/92
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INTLITE
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10
04/10/92
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TEMP2
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04/10/92
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MAXACT
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INTLITE
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04/11/92
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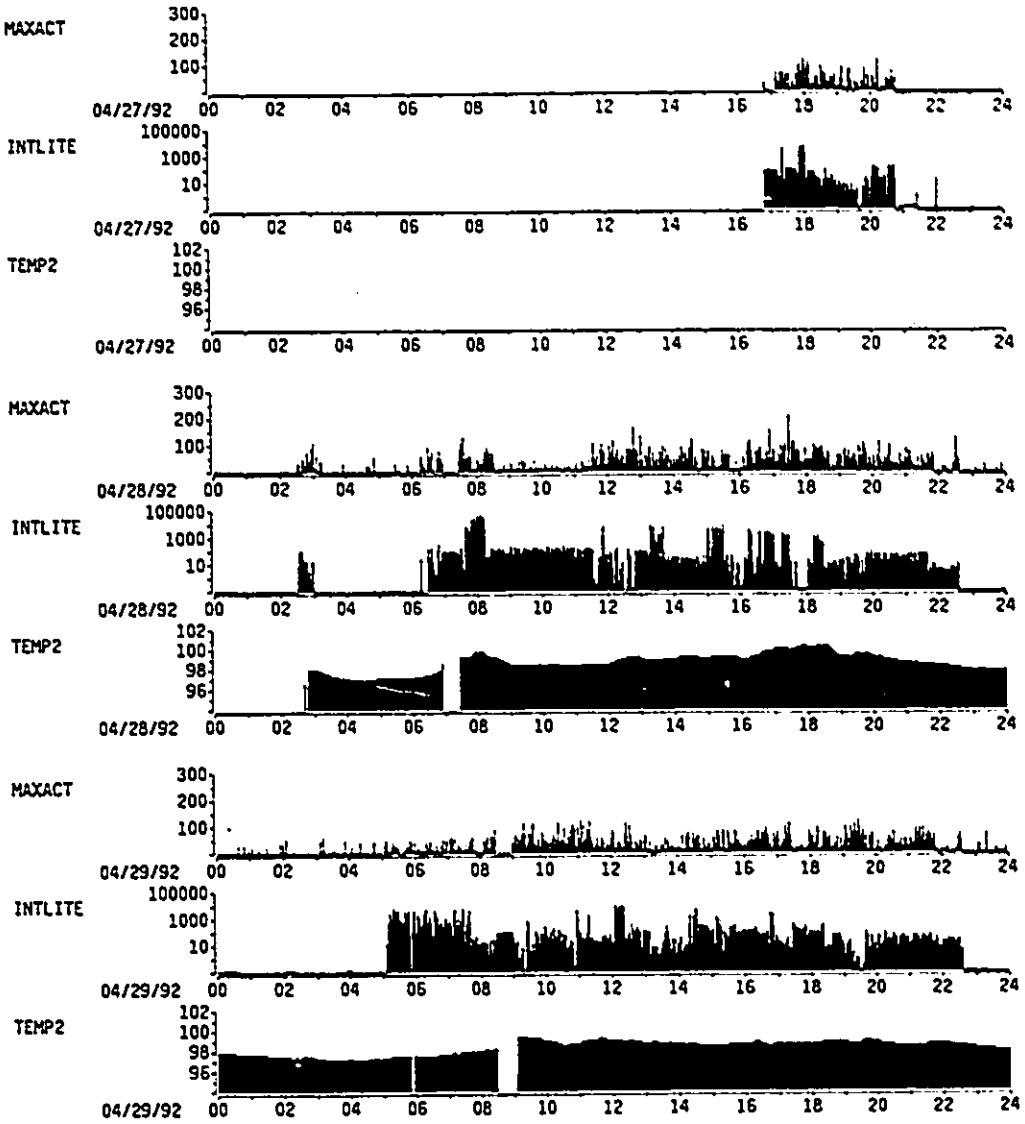
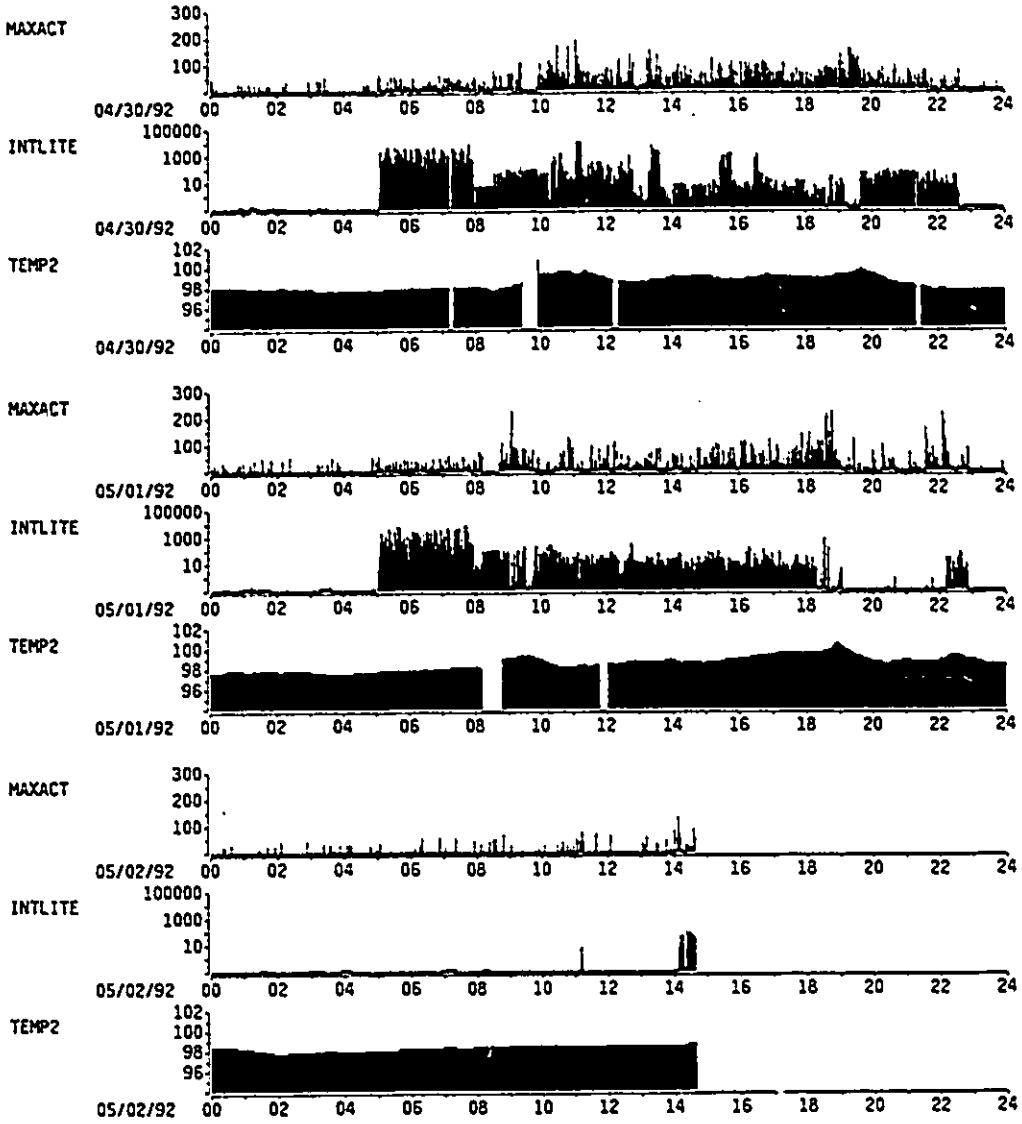
Actillume data: Subject 3, ML

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INTLITE
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TEMP2
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04/30/92
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MAXACT
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INTLITE
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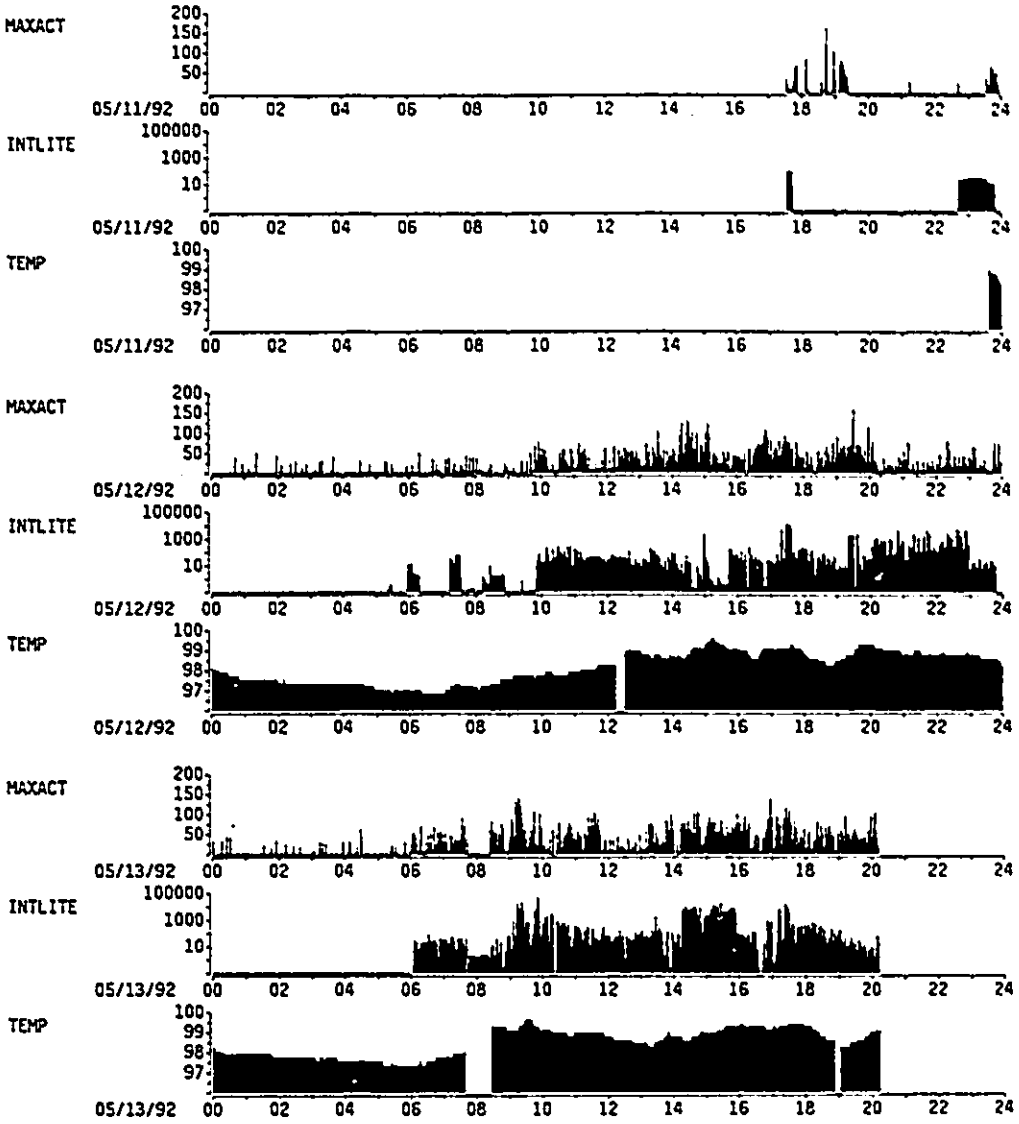
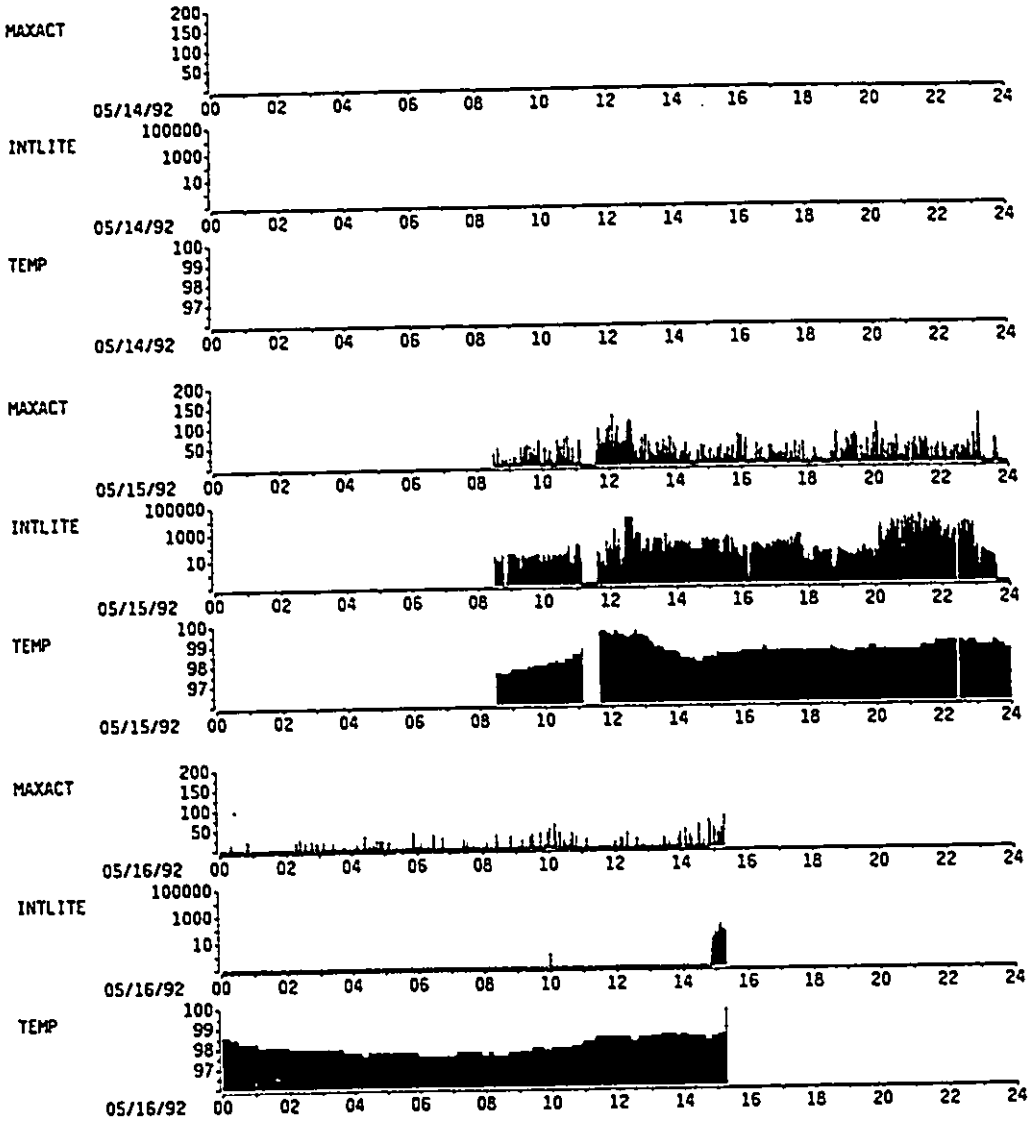
Actillume data: Subject 3, EL

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00 02 04 06 08 10 12 14 16 18 20 22 24