

# **Sleep/Wake Cycle Disturbance in Alzheimer's Disease: How Much Is Due to an Inherent Trait?**

**JEROME A. YESAVAGE, JOY L. TAYLOR, HELENA KRAEMER,  
ART NODA, LEAH FRIEDMAN, AND JARED R. TINKLENBERG**

---

**ABSTRACT.** Major advances in understanding the physiology and genetics of circadian rhythm in the past decade challenge the researcher of sleep/wake disorders in Alzheimer's disease (AD) to distinguish patient characteristics stable across the course of illness ("traits") from characteristics that vary with stage of illness ("states"). A components-of-variance approach with a repeated measures model was used to examine the between-subjects variance over time ("trait") vs. within-subjects ("state") variance in 42 patients with probable AD followed, on average, over 2 years on actigraphic sleep/wake measures. Mental status scores indexed stage of illness. Actigraphic measures of sleep efficiency and circadian rhythmicity appeared predominantly "trait," with between-individual differences accounting for over 55% of variance compared to the less than 5% of variance related to stage of cognitive impairment. We discuss how "state-trait" analyses can be helpful in identifying areas of assessment most likely to be fruitful objectives of physiologic and genetic research on sleep/wake disturbance in AD.

**KEYWORDS:** Alzheimer's disease; dementia severity; longitudinal studies; sleep/wake disturbances; circadian rhythm

Our aim in identifying sources of variability in sleep/wake patterns in Alzheimer's disease (AD) is motivated by the need to identify phenotypes, or characteristics that are stable over the course of illness, in the hope that this will lead to the identification of the

genetic factors that underlie these phenomena. Recent studies of sleep/wake cycles indicate that probably fewer than a dozen genes in humans play a major role in these phenomena (King et al., 1997). New breakthroughs in discovering the etiology of sleep/wake disorders in AD and in designing effective treatments for them depend upon properly associating genetic factors with the

---

From the Department of Veterans Affairs Health Care System, Palo Alto, California, US (J. A. Yesavage, MD; J. L. Taylor, PhD; and J. R. Tinklenberg, MD), and the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, US (J. A. Yesavage; J. L. Taylor; H. Kraemer, PhD; A. Noda, MS; L. Friedman, PhD; and J. R. Tinklenberg).

*Offprints.* Requests for offprints should be directed to Jerome Yesavage, MD, Palo Alto VA Health Care System (151Y), 3801 Miranda Avenue, Palo Alto, CA 94304, US. email: yesavage@stanford.edu

clinical features or phenotypes they determine. Fundamental to this endeavor is determining whether a clinical variable measured at one point in time reflects a stable individual trait that may be genetically based, or a patient's state that fluctuates with stage of the illness.

In this article we contrast trait and state variables: (a) Variables that are stable and differentiate subjects from each other have been called "trait" variables (see Eysenck, 1983, for a review). For variables that are pure traits, any within-subject variation over time is, by definition, due to random error of measurement; therefore cross-sectional measurement at any stage of illness can be adequate for their assessment. Trait variables provide a convenient, straightforward means of identifying subgroups of AD patients in whom etiology, course, or response to treatment may differ. Such variables might include gender, year or place of birth, or specific genotypes. (b) Other variables, sensitive to change within the individual, have been called "state" variables. In the case of state variables, there is at least some variability within each patient that can be explained by stage of disease or other factors that vary systematically with time. When a symptom or behavior is stage-related, longitudinal assessment is the best means of tracking the onset of the symptom or its development. Although some variables may be predominantly "trait" or predominantly "state," other variables might include characteristics of both.

Recently, Kraemer and associates (1994) proposed a methodology to separate the "state" and "trait" aspects of several types of measures commonly used in psychiatric research. In doing

so, they emphasized that the "state-trait" aspect of a variable is related to a *time span* of interest and to a *population* of interest. They implemented the state-trait approach, which necessarily requires repeated measures on each subject, by using a components-of-variance model based on analysis of variance (ANOVA). The model can be used to distinguish the proportion of total variance in the system associated with traits from that associated with states, and from that associated with error of measurement. Discovery of substantial trait variance should lead to subsequent examination of relevant sources of such variation, such as sex, education, age of onset, family history, and especially genetic status. In this presentation we examine two classic rest/activity variables assessed over the course of AD and suggest that these measures may demonstrate a substantial amount of "trait" characteristics.

## METHOD

### Subjects

The 42 subjects in this report were patients who were participants in an ongoing longitudinal study of AD at the Stanford/Veterans Affairs NIA Alzheimer's Disease Core Center. Center inclusion criteria at the time of entry were: (a) diagnosis of probable AD by NINCDS-ADRDA criteria (McKhann et al., 1984) and (b) a score of 15 or higher at entry on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). Patients were excluded if they had active major medical problems (e.g., congestive heart failure or recent life-threatening cancer) that would have made participation in an intensive longitudinal study difficult. All eligible

patients were recruited as soon as possible after the diagnosis of probable AD, with written informed consent obtained from patients or their caregivers. To determine the clinical diagnosis, each patient had medical, psychiatric, neurological, neuroimaging, and neuropsychological assessments. Based on these evaluations, a consensus diagnosis was reached by an interdisciplinary team including one to three physicians and at least two other experienced clinicians.

For 42 subjects, we collected 181 actigraphic recordings from which we calculated the amplitude of their rest/activity circadian rhythm. We also were able to derive sleep efficiency (SE) information from 154 recordings of a subset of 34 of the subjects whose caregivers also completed daily sleep logs. The sample as a whole was highly educated (47.6% college graduates), was predominantly non-minority (81.0% White), and contained more men (61.9%) than women. At entry, the average age was 70.8 years ( $SD = 7.5$ ). All subjects were initially home-dwelling or living in board-and-care homes; i.e., none were in skilled nursing facilities at entry. To be included in the state-trait analysis, subjects must have been tested during at least two stages of cognitive impairment, as defined as a decline from one stage of the illness to another. Staging is described below.

## Measures

**MMSE Staging.** The MMSE, administered every 6 months, was used to describe the subject's stage of cognitive impairment at each occasion activity data were collected. In earlier work, we developed a staging system for AD based on the MMSE (Kraemer et al., 1998). We grouped MMSE scores to form five levels of severity:

Stage 1	Early	MMSE = 24-30
Stage 2	Mild	MMSE = 15-23
Stage 3	Moderate	MMSE = 8-14
Stage 4	Moderately severe	MMSE = 4-7
Stage 5	Severe	MMSE = 0-3

This approach based on the MMSE yields results that are similar to the staging method based upon the commonly used Global Deterioration Scale (GDS; Reisberg et al., 1982). For example, a MMSE Stage 5 would be approximately equivalent to a GDS Stage 7. MMSE staging may provide an alternative to the widely used GDS staging when the latter is not available.

The majority of the subjects spanned two MMSE stages at the times of their actigraphic recordings. However, for the circadian rest/activity amplitude data, there were seven subjects who spanned three stages, two who spanned four stages, and one who spanned all five stages. Of those for whom we were able to calculate SE, six spanned three stages and three spanned four stages. Of the 42 subjects, 15 entered the actigraphic recording protocol at MMSE Stage 1, 19 at Stage 2, 6 at Stage 3, and 2 at Stage 4. At the end of the study, 10 were at Stage 2, 16 were at Stage 3, 6 at Stage 4, and 10 at Stage 5.

**Actigraph.** Rest/activity data were collected at 6-month intervals by means of a wrist-worn, watch-size, ambulatory motion-detecting device, the Actigraph (Ambulatory Monitoring Systems, Inc., Ardsley, NY). The Actigraph was set to record motion in 30-second epochs. These activity data were used to measure circadian rhythmicity of rest and activity and, when there was a caregiver able to complete daily sleep logs, to infer nighttime amounts of sleep and wake. Patients were asked to wear the Actigraph 24

hours a day on their nondominant wrists for 5 consecutive days. Caregivers completed a sleep log each day noting the patient's in- and out-of-bed times. Caregivers and patients were instructed to remove the Actigraph only for bathing or swimming.

Measures of circadian rest/activity were computed by using a least-squares method to fit the Actigraph data to a cosine curve. The amplitude of the fitted curve was our primary measure of circadian rhythmicity; larger amplitudes suggest a more robust circadian rhythm. Measures of nighttime sleep/wake behavior, in particular, SE, or the ratio of total sleep time to total time in bed, were obtained by computer scoring (ACTION software version 1.32). The algorithm, supplied by the manufacturer of the Actigraph, scores the Actigraph recordings following entry of subjects' evening bed times and final morning out-of-bed times. The scores used in the data analyses were averages of the consecutive days of actigraphy; night-to-night variability was not examined in this report. Not all data were usable because of occasional technical failures of the device, and the amount of Actigraph data collected varied across subjects depending on their compliance, but at least 80% of subjects had at least 5 or more days of data per recording session. Subjects' average length of follow-up was 817 days ( $SD = 494$ ; 25th percentile = 436, 50th percentile = 753, 75th percentile = 1,115) over which time the average MMSE score fell 7.8 points ( $SD = 6.0$ ; 25th percentile = 4, 50th percentile = 7, 75th percentile = 12) from a mean of 18.6 ( $SD = 5.8$ ; 25th percentile = 24, 50th percentile = 19, 75th percentile = 15) to a mean of 10.8 ( $SD = 6.9$ ; 25th percentile = 16, 50th percentile = 10.5, 75th percentile = 5).

## Procedure

Patients were asked to begin the Actigraph recordings immediately following a clinic visit. Cognitive measures were administered to all center patients at each 6-month visit. These data were collected by psychiatrists and nurses trained to do a standardized assessment, with the assistance of a trained psychology technician. When patients became institutionalized or could no longer come to the clinic, an outreach nurse administered cognitive measures at the patient's residence. Follow-up assessments ceased when patients scored a zero on the MMSE at two successive visits.

## Analysis

The basic design of this study is a two-way layout (Subjects x Stage); however, not all subjects had observations in all stages and some had multiple observations within a stage. The total variance is partitioned into portions associated with the main effect of Subjects (Trait), the main effect of Stage (State: Stage), the interactive effect of subjects and stage (State: Other), and variation within a cell (for the purposes of this study: Error).

To accomplish this objective, we used a two-step approach. In the first step, we used a one-way ANOVA to estimate the percentage of total variance within and between cells. The within-cell variance reflects observer or instrument error as well as short-term inconsistency of subjects' responses. If the total variance is due largely to such error, there is little true variance attributable either to trait or state, the issues here of primary importance, in which case the contributions of those sources will be poorly esti-

mated. In the second step, we averaged multiple observations of a subject within a stage so that each subject had one score for each stage. We then performed a two-way ANOVA (Subjects x Stages) and estimated the percentage of total variance due to Trait and State: Stage, with the residual labeled State: Other.

## RESULTS

### True Variance: State-Trait Aspects

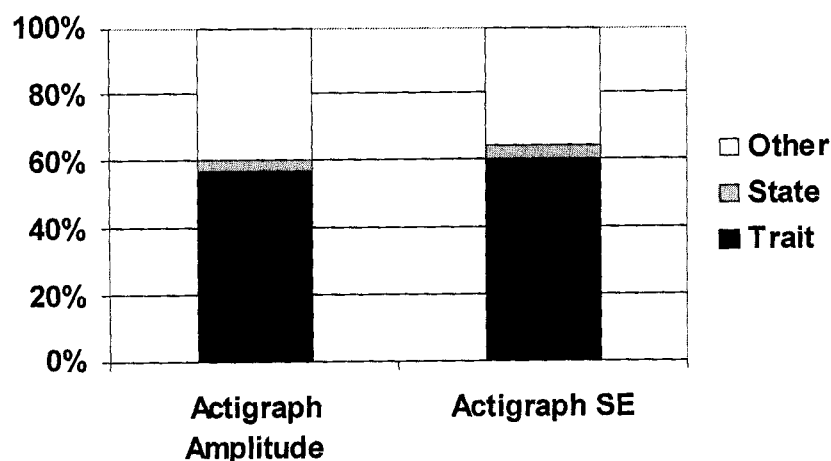
The state-trait aspects of the variables are summarized in Figure 1, which shows the percentage of true variance attributable to (a) trait, (b) MMSE stage, and (c) other states, i.e., states that might be related to environmental or patient states unrelated to MMSE stage. The actigraphic measures of SE and circadian rhythm amplitude appeared predominantly trait-like, with approximately 55% to 60% of true variance attributable to traits, or stable between-subject differences. The patterns of response as a function of MMSE stage for these variables are presented in Table 1. As indicated in the table, SE scores declined from a median of 79% in Stage 1 to about 75% in Stage 3, then to 68% in Stage 5. As presented in Figure 1, we found that SE and amplitude of circadian rhythm were not substantially stage-related (< 5% Stage).

## DISCUSSION

Prior studies of sleep/wake variables in AD have suggested a deterioration of function with increasing duration of illness (Ancoli-Israel et al., 1994). This deterioration is also consistent with the mean values by stages data in Table 1.

We have previously reported significant longitudinal decline of sleep/wake parameters in the same patients who are the subjects of the current analysis (Yesavage et al., 1998). However, the current analysis suggests that this "state" component of true variance, though "significant," may be relatively small when compared to the "trait" component. The predominant component in patients' sleep was the "trait" aspect, which signals relatively large and persistent patient differences. For example, patients' initial, Stage 1 SE scores ranged from a high of 93% to a low of 49%. What this really says is that although there is some deterioration of AD patients' SE and circadian rhythm amplitude, bad sleepers who develop AD remain bad sleepers and get a little worse and good sleepers who develop AD remain good sleepers but perhaps not quite as good.

We caution that the state-trait estimates are preliminary and need to be confirmed when longer follow-ups of more patients are available. Nonetheless, these results can be contrasted with results on cognitive measures such as the GDS or Alzheimer's Disease Assessment Scale, which would show over a similar time period as much as an 80% "state" characteristic. The subjects of this study were all outpatients; hence, these results may not be the same as those seen in patients in a nursing home. Even within an entirely outpatient population, the actigraphic scores varied to some degree within the same patient over time independently of MMSE stage. This variation can be explained by the "other" components of variance, observed to be 35% to 40% of the true variance. Such within-patient variation may occur in response to factors not controlled for in this obser-



**Figure 1.** Percent of true variance attributable to trait, stage, and other state(s). SE = sleep efficiency.

**TABLE 1.** Actigraphic Scores by MMSE Stage: 25th Percentiles, Medians, 75th Percentiles, Number of Patients, and Variance Estimations

Measure	MMSE Stage					Variance Estimation		
	1	2	3	4	5	% Trait	% Stage	% Other
Amplitude of rest/activity circadian rhythm								
25%ile	36.7	37.1	38.1	37.3	33.6	57 <sup>a</sup>	3 <sup>b</sup>	40
Median	49.3	44.3	44.7	45.3	41.2			
75%ile	50.7	50.9	55.5	52.9	50.2			
<i>n</i>	15	32	27	14	10			
Sleep efficiency (0–100%)								
25%ile	69.6	71.2	68.6	53.2	50.0	60 <sup>c</sup>	4 <sup>d</sup>	36
Median	78.8	78.6	75.1	71.9	68.4			
75%ile	82.1	83.4	85.8	78.2	80.3			
<i>n</i>	12	28	22	11	7			

Note. MMSE = Mini-Mental State Examination.

<sup>a</sup> $F_{4,41} = 4.33; p < .0001$ . <sup>b</sup> $F_{4,41} = 2.70; p < .05$ . <sup>c</sup> $F_{4,33} = 5.00; p < .0001$ . <sup>d</sup> $F_{4,33} = 2.81; p < .05$ .

vational study, e.g., changes within the patients' home settings, additional illness, varying patient drug use in different MMSE stages, or differences in degree of family support. Although in this article we examined change *over stages* of cognitive impairment, our research center recently reported a significant change *over time* in SE of  $8\% \pm 12.9\%$  ( $p < .002$ ), measured by

computing the difference in SE between two time points that were a minimum of 6 months apart (Yesavage et al., 1998). In that analysis, neither the duration of follow-up nor the stage of patient's illness at either time point was considered. In contrast, the present analysis evaluates changes over stages, acknowledging that different patients may spend different

lengths of time in different stages and that patients need to be matched on stage in order to track the effects of the progression of AD on sleep/wake and circadian rest/activity measures.

At any stage of AD, pathology in the suprachiasmatic nucleus (SCN) could be a cause of individual differences in the integrity of the circadian system of rest/activity and differences in patterns of sleep/wake. Although different areas of the brain and/or body may be able to generate circadian rhythms, a small group of neurons in the anterior hypothalamus, the SCN, are thought to synchronize a number of physiological rhythms to induce a single circadian oscillation in mammals (see Mirmiran et al., 1992). Light conveyed to the SCN via the retina to hypothalamic pathways is the main factor in the daily entrainment of the endogenous activity of the SCN to 24-hour time cues. Swaab and colleagues (1998) reported a marked decrease in the total number of arginine vasopressin-positive (AVP) and vasoactive intestinal polypeptide (VIP) neurons and SCN volume in 80-100-year-old normals compared to younger ones. This is in accordance with a decreased number of AVP-positive and VIP-immunoreactive (IR) neurons found in aged rats (Chee et al., 1988). Thus, older individuals may already develop significant SCN pathology before they manifest AD. This pathology may form the anatomical basis for the "trait"-like aspect of the sleep/wake phenomenon we found in our study. On the other hand, other work, including Swaab and colleagues (1998) and Stopa and colleagues (1999), found further reduction in the total number of these same neurons in AD patients compared to age-matched nondemented controls. Such AD-related changes may form the anatomical basis

for the "state"-like aspects of the sleep/wake phenomena we found in our study.

What could be the genetic basis of a "trait" component of sleep/wake disturbances and does it offer any insights into potential treatments? A limited number of genes have been reported to underlie circadian rhythmicity across several species (King et al., 1997). Variation within the relatively small number of circadian genes could result in several relevant phenotypes, including difficulty in entraining to external cues (e.g., delayed or advanced sleep-phase syndromes). The issue of the potential impact of variation within human circadian genes is emphasized by a recent study showing that variation in the human CLOCK gene may be associated with differences in diurnal preference (Katzenberg et al., 1998). Variations in the human CLOCK and other genes may well affect sleep/wake measures in AD patients and may also affect the potential of individual patients to respond to interventions such as bright light therapy.

Poor sleep is a significant clinical problem in AD and has been found to be associated with what is now termed behavioral and psychological symptoms of dementia (BPSD) and invites attempts at intervention (Ancoli-Israel et al., 1994; Friedman et al., 1997; <http://www.thecyberfactory.com/bpsd/>). Age-related declines in rhythm amplitudes and AVP-IR cell loss could be restored after stimulating the SCN of older animals by housing them under high light conditions (Lucassen et al., 1995; Witting et al., 1993). Furthermore, it has been suggested that in the case of humans, bright light interventions designed to improve sleep may in turn improve behavior

(Mishima et al., 1994; Satlin et al., 1992). Better understanding of sleep/wake "traits" in AD patients may ultimately also allow us to identify patients most likely to benefit from interventions such as bright light therapy.

## CONCLUSION

In this article we suggest that much of the variance associated with sleep/wake disturbances is a "trait" of the AD patient. Although not all variance is "trait," this finding suggests a strong physiological, if not genetic, basis for this characteristic beyond the simple progression of the disease. There are several candidates for possible physiological and genetic mechanisms underlying this "trait." Better understanding of such mechanisms may form the basis of more effective interventions for AD patients who have sleep/wake disturbances.

## REFERENCES

- Ancoli-Israel, S., Klauber, M. R., Gillin, J. C., Campbell, S. S., & Hofstetter, C. R. (1994). Sleep in non-institutionalized Alzheimer's disease patients. *Aging Clinical Experimental Research*, *6*, 451-458.
- Chee, C. A., Roozendaal, B., Swaab, D. F., Goudsmit, E., & Mirmiran, M. (1988). Vasoactive intestinal polypeptide neuron changes in the senile rat suprachiasmatic nucleus. *Neurobiology of Aging*, *9*, 307-312.
- Eysenck, H. J. (1983). Cicero and the state-trait theory of anxiety: Another case of delayed recognition. *American Psychologist*, *38*, 114-115.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189-198.
- Friedman, L., Kraemer, H. C., Zarcone, V., et al. (1997). Disruptive behavior and actigraphic measures in home-dwelling patients with Alzheimer's disease: Preliminary report. *Journal of Geriatric Psychiatry and Neurology*, *10*, 58-62.
- Katzenberg, D., Young, T., Finn, L., Lin, L., King, D. P., et al. (1998). A CLOCK polymorphism associated with human diurnal preference. *Sleep*, *21*, 569-576.
- King, D. P., Zhao, Y., Sangoram, A. M., et al. (1997). Positional cloning of the mouse Clock gene. *Cell*, *89*, 641-653.
- Kraemer, H. C., Gullion, C. M., Rush, A. J., Frank, E., & Kupfer, D. J. (1994). Can state and trait variables be disentangled? A methodological framework for psychiatric disorders. *Psychiatry Research*, *52*, 55-69.
- Kraemer, H. C., Taylor, J. L., Tinklenberg, J. R., & Yesavage, J. A. (1998). The stages of Alzheimer's disease—A reappraisal. *Dementia and Geriatric Cognitive Disorders*, *9*, 299-308.
- Lucassen, P. J., Hofman, M. A., & Swaab, D. F. (1995). Increased light intensity prevents the age related loss of vasopressin-expressing neurons in the rat suprachiasmatic nucleus. *Brain Research*, *693*, 261-266.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., et al. (1984). Clinical diagnosis of Alzheimer's disease: A report of the NINCDS-ADRDA workgroup under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*, 939-944.
- Mirmiran, M., Swaab, D. F., Kok, J. H., Hofman, M. A., Witting, W., et al. (1992). Circadian rhythms and the suprachiasmatic nucleus in perinatal development, aging and Alzheimer's disease. *Progress in brain research* (pp. 151-162). Amsterdam: Elsevier.
- Mishima, K., Okawa, M., Hishikawa, Y., Hozumi, S., Hori, H., et al. (1994). Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta Psychiatrica Scandinavica*, *89*, 1-7.



- Reisberg, B., Ferris, S., de Leon, M. J., & Crook, T. (1982). The Global Deterioration Scale (GDS): An instrument for the assessment of primary degenerative dementia (PDD). *American Journal of Psychiatry*, *139*, 1136-1139.
- Satlin, A., Volicer, L., Ross, V., Herz, L., & Campbell, S. (1992). Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *American Journal of Psychiatry*, *149*, 1028-1032.
- Stopa, E. G., Volicer, L., Kuo-Leblanc, V., Harper, D., Lathi, D., et al. (1999). Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. *Journal of Neuropathology & Experimental Neurology*, *58*, 29-39.
- Swaab, D. F., Lucassen, P. J., Salehi, A., Scherder, E. J., van Someren, E. J., et al. (1998). Reduced neuronal activity and reactivation in Alzheimer's disease. *Progress in Brain Research*, *17*, 343-377.
- Witting, W., Mirmiran, M., Bos, N. P., & Swaab, D. F. (1993). Effect of light intensity on diurnal sleep-wake distribution in young and old rats. *Brain Research Bulletin*, *30*, 157-162.
- Yesavage, J. A., Friedman, L. F., Kraemer, H. C., Noda, A., Wicks, D., et al. (1998). A follow-up study of actigraphic measures in home-residing Alzheimer's disease patients. *Journal of Geriatric Psychiatry and Neurology*, *11*, 7-10.

*Acknowledgments.* We express appreciation to our clinical research staff: Terry Miller, MD, Helen Davies, RNMS, and Aimee Mott, for clinical testing and assessments. Special appreciation is expressed to Deryl Wicks who organized the longitudinal Actigraph follow-up and quantification. This research was supported by National Institute of Mental Health grant MH40041, National Institute on Aging grant AG17824, the Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), and the Medical Research Service of the Department of Veterans Affairs.