

# Differential Circadian Rhythm Disturbances in Men with Alzheimer Disease and Frontotemporal Degeneration

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**Background:** Caregiver exhaustion is a frequent consequence of sleep disturbance and rest-activity rhythm disruption that occurs in dementia. This exhaustion is the causal factor most frequently cited by caregivers in making the decision to institutionalize patients with dementia. Recent studies have implicated dysfunction of the circadian pacemaker in the etiology of these disturbances in dementia.

**Methods:** We studied the activity and core-body temperature rhythms in a cohort of 38 male patients with a clinical diagnosis of probable Alzheimer disease (AD) approximately 2 years before death. These patients were later given a confirmed diagnosis of AD (n=23), frontotemporal degeneration (FTD) (n=9), or diffuse Lewy body disease (DLB) with mixed AD or FTD pathologies (n=6) after autopsy and neuropathological examination. Physiological rhythms of patients with AD and FTD were then

compared with a group of normal, elderly men (n=8) from the community.

**Results:** Alzheimer patients showed increased nocturnal activity and a significant phase-delay in their rhythms of core-body temperature and activity compared with patients with FTD and controls. The activity rhythm of FTD patients was highly fragmented and phase-advanced in comparison with controls and apparently uncoupled from the rhythm of core-body temperature.

**Conclusions:** Patients with AD and patients with FTD show different disturbances in their rhythms of activity and temperature compared with each other and with normal elderly patients.

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SLEEP DISTURBANCES are common and disruptive symptoms of disorders characterized by dementia. The sleep-pattern disturbances seen in this population include initial and terminal insomnia, frequent nocturnal awakenings, and sleep reversal<sup>1,2</sup> and exceed those found in healthy elderly volunteers in both frequency and duration.<sup>3</sup> Insomnia in demented patients imposes a great burden on caregivers, impedes their ability to function normally, and is the leading cause of institutionalization in individuals with a dementing illness.<sup>4,5</sup> Studies of motor behavior suggest that disruption of the sleep-wake cycle may be caused by a decreased ability to maintain a stable pattern of diurnal arousal and nocturnal quiescence—a pattern normally influenced by circadian rhythmicity.<sup>6-9</sup>

Circadian control of the timing of the sleep-wake cycle is mediated by the endogenous circadian rhythm generated by the suprachiasmatic nuclei (SCN) of the hypothalamus.<sup>10-13</sup> Core-body tempera-

ture is the most direct and measurable manifestation of this output,<sup>14</sup> especially under constant routine conditions.<sup>15</sup> Many subcortical structures, such as the basal forebrain, dorsal and central superior raphe nuclei, and the reticular formation of the pons and medulla, also seem to be involved in the initiation of sleep and the oscillation between REM and non-REM states.<sup>16-22</sup> Current thinking maintains that there is a dynamic interplay between the circadian pacemaker in the SCN modulating arousal (process C) and flexible homeostatic influences modulating sleep tendency (process S) possibly based in these other subcortical structures.<sup>12,23</sup> All of these structures potentially could be damaged as a consequence of Alzheimer disease (AD)<sup>16</sup> and frontotemporal degenerative dementias (FTD),<sup>24</sup> and their deterioration could explain many sleep architecture and continuity changes seen in these illnesses.<sup>1,25</sup>

Alzheimer disease and FTD are both progressive, degenerative dementias characterized by global loss of cognitive abil-

## SUBJECTS AND METHODS

### SUBJECTS

Thirty-eight men with dementia with a mean $\pm$ SE age of 70.2 $\pm$ 1.0 years, an age of onset of 60.7 $\pm$ 1.1 years, and a duration of illness at the time of recording of 11.8 $\pm$ 0.7 years were sampled from a clinical population at the EN Rogers Memorial Veterans Hospital, Bedford, Mass. All subjects were evaluated by a board-certified psychiatrist (L.V.) on enrollment and met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations criteria for probable AD.<sup>26</sup> They had no lifetime history of major affective illness, schizophrenia, or substance abuse, except for 4 subjects who had some background of alcohol abuse yet met criteria for probable AD. All dementia subjects at the time of physiological recording were severely impaired, ambulatory and nonambulatory, Reisberg stage 5 to 6<sup>35</sup> patients. They required 24-hour institutional care, were free from significant intercurrent illnesses, and were taking no antipyretic medication for at least 24 hours before the physiological recordings. The comparison subjects for the physiological recordings were 8 elderly male volunteers from the community recruited through the Harvard Project on Aging and the Massachusetts Institute of Technology's Clinical Research Center. They had a mean $\pm$ SE age of 72.8 $\pm$ 2.1 years and no evidence of dementia, as verified by Mini-Mental State Examination and clinical evaluation by a board-certified psychiatrist (A.S.). They otherwise met all the same criteria for inclusion as the dementia subjects. Controls were studied at the Massachusetts Institute of Technology's Clinical Research Center, which closely simulates a hospital environment. They were admitted to the unit the day the study began.

### PROCEDURES

#### Circadian Studies

After institutional review of the project and the receipt of informed consent from the control subjects and the next-of-kin of the dementia subjects, physiological rhythms were studied for 72 hours, beginning at noon on the first study day, using ambulatory monitors. The unit schedule for patients and controls was lights out at 10 PM and lights on at 6 AM. Controls were allowed free mobility, including outside the unit during the study. Patients were allowed the same privileges as controls as far as possible within the constraints of their illness. Motor activity was recorded using an AM-16 activity monitor (AMI, Ardsley, NY), worn on the nondominant ankle and sensitive to accelerations of 0.1g (1 activity count) by the mechanical action of a piezoelectric bender and counterweight. Activity counts were accumulated in 5-minute epochs, and the resultant quantity was then written to memory. Temperature was measured by a temperature sensitive thermistor (Series 400; YSI Inc, Yellow Springs, Ohio), accurate to 0.1°C and placed in the rectum to a depth of 10 cm. This probe was connected to an ambulatory temperature monitor (Mini-Logger; Mini-Mitter Corp, Sun River, Ore), which sampled the temperature every 6 minutes and wrote it to memory for later retrieval. All nursing care and other patient interventions were noted for later editing of data artifacts, and all temperature and activity records were at least 80% complete.

#### Diagnosis at Autopsy

Physiological data were recorded 1.74 $\pm$ 0.21 (mean $\pm$ SD) years before death and autopsy. All brains were subjected to a standardized neuropathologic examination. Brains were fixed for at least 4 weeks in 10% neutral buffered formalin

ity and accompanied by a wide range of noncognitive symptoms. Frontotemporal degenerative dementias often present initially with progressive aphasia and personality changes, while, in the initial stages of the illness, memory remains intact. In AD, memory loss is often the first symptom reported and personality remains intact for a longer duration. As the illnesses progress, symptom presentations become more similar between these 2 forms of dementia, and a recent study found that the specificity of the diagnosis of probable AD, using the best criteria available,<sup>26</sup> was 0.23.<sup>27</sup> Therefore, these 2 dementias become virtually indistinguishable from each other without pathological examination. Such examination reveals either the presence of amyloid plaques sufficient for the diagnosis of AD or the neuronal loss of the frontal and temporal regions, without plaque formation, which is indicative of FTD.

There are several lines of evidence supporting the hypothesis that changes in the endogenous circadian system caused by a dementing illness<sup>28</sup> lead to the disruption of the rest-activity and sleep-wake rhythms. Our group has shown that there is a phase-delay in the circadian rhythm of temperature and activity in patients with probable AD and a reduced synchronization between

rhythms of temperature and activity.<sup>8</sup> Patients with dementia also show specific patterns of destruction in the SCN, which could result in a disruption of these circadian rhythms.<sup>29,30</sup> Finally, light treatment, which is effective in changing the circadian rhythm,<sup>14</sup> may be effective in treating sleep-wake disturbances in these patients.<sup>7,31-33</sup> The current work improves on these earlier studies by examining antemortem activity and temperature data in the light of postmortem diagnosis made approximately 2 years later.

There are at least 2 possible explanations for the putative chronobiologically based sleep and rest-activity rhythm disturbances in patients with dementia. The first hypothesis is that the institutions in which these patients were studied caused the chronobiological disturbance by providing insufficient signals or *zeitgebers* to entrain (coordinate temporally with the environment) the patient's circadian rhythms. Low light levels during the day and increased nocturnal lighting, endemic to these institutions,<sup>32</sup> and also found in the home environment,<sup>34</sup> may make it difficult to achieve robust entrainment to the environment. With this "environmental" hypothesis, no dysfunction of the circadian system is necessary to explain the rest-activity and sleep-wake dis-

to standardize shrinkage during fixation. Fourteen brain areas were routinely sampled based on their suitability for diagnosing AD, FTD, and dementia with Lewy bodies (DLB). The diagnosis of AD was guided by the consensus criteria established by the Consortium to Establish a Registry for Alzheimer's Disease<sup>36</sup> and by the work of Braak and Braak,<sup>37</sup> both endorsed by the International Working Group from the National Institute on Aging and the Reagan Institute.<sup>38</sup> Diagnosis of DLB or Parkinson disease was made using criteria established by the Dementia With Lewy Bodies International Workshop.<sup>39</sup> Significant vascular disease, a diagnosis of exclusion, was based on the criteria outlined in the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences International workshop.<sup>40</sup> The diagnosis FTD refers to non-Alzheimer degenerative disorders that primarily affect the frontal and temporal lobes. This category includes cases that fit the classic description of Pick disease with severe cortical atrophy, neuronal loss, gliosis, Pick bodies, and ballooned neurons, as well as cases of frontal and/or temporal atrophy, with or without ballooned neurons, without Pick bodies. This classification scheme also includes most cases of corticobasal ganglionic degeneration, frontotemporal dementia, non-Alzheimer frontal lobe dementia, chromosome 17–linked dementia, and progressive subcortical gliosis.

## DATA ANALYSIS

Representative recordings of activity and temperature in the 3 diagnostic groupings are shown in **Figure 1**. Motor activity was assessed for mean diurnal (6 AM to midnight) and nocturnal (midnight to 6 AM) activity (activity counts per 5-minute epoch). Gross motor activity was also assessed using the M10 and L5 indices.<sup>6</sup> The M10 is the mean activity counts per hour of the 10 most active hours in the

24-hour period. The L5 is the mean activity counts per hour of the 5 least active hours in the 24-hour period.

Interdaily stability, a periodogram-based algorithm measuring day-to-day stability of the rhythm, and intradaily variability, a measurement of the fragmentation of the activity rhythm that assesses the period-to-period variability of the rhythm, were used as nonparametric measures of the circadian rhythm of motor activity.<sup>6</sup> These methods of activity analysis make no assumptions about the shape of the data or the continuity of the function, and therefore may be more sensitive than cosinor and other parametric methods.<sup>32</sup>

Cosinor analysis was used to model a circadian rhythm to the temperature and activity data.<sup>41</sup> Cosinor analysis makes a mathematical model of the data by estimating the mesor (the point around which the model oscillates), amplitude (the distance from the mesor to the peak), and phase (the time of the model peak) of the circadian rhythm, and calculates a goodness-of-fit (the square of the least squares correlation [ $R^2$ ]) of the model to the data. For these analyses, we fixed the frequency at 1 cycle per day and performed a 2 harmonic fit (1 and 2 cycles per day) to the activity and temperature data. To control for differing overall activity levels between subjects, we measured amplitude of the activity rhythm as relative amplitude (amplitude per mesor).

Three groups (control, AD, and FTD) were directly compared in this study using a between-subjects analysis of variance with Tukey post hoc comparisons. The significance level for all tests was set at  $\alpha = .05$  (2-tailed). In addition, dementia patients were also tested for systematic differences between the different diagnoses in age, age of onset of illness, duration of illness, and length of hospitalization. All values are reported as mean  $\pm$  SE except where noted. Patients who did not evidence a circadian rhythm of activity or temperature were also excluded from further analysis if an F test comparison of the cosinor fit to a mesor fit had a value  $P > .05$ .<sup>41</sup>

turbance seen in patients with dementia. The second hypothesis is that the circadian system in these patients is selectively impaired, and, as a result, they are unable to maintain entrainment. If the first hypothesis is true, there should be no difference between the different diagnostic categories, and impairments to the circadian rhythm should be similar across all patients. If the differences are caused by central changes related to the disease process, then differences may emerge between the diagnostic groupings. Understanding the origin of these circadian changes then may have diagnostic utility and indicate proper treatment strategies.

## RESULTS

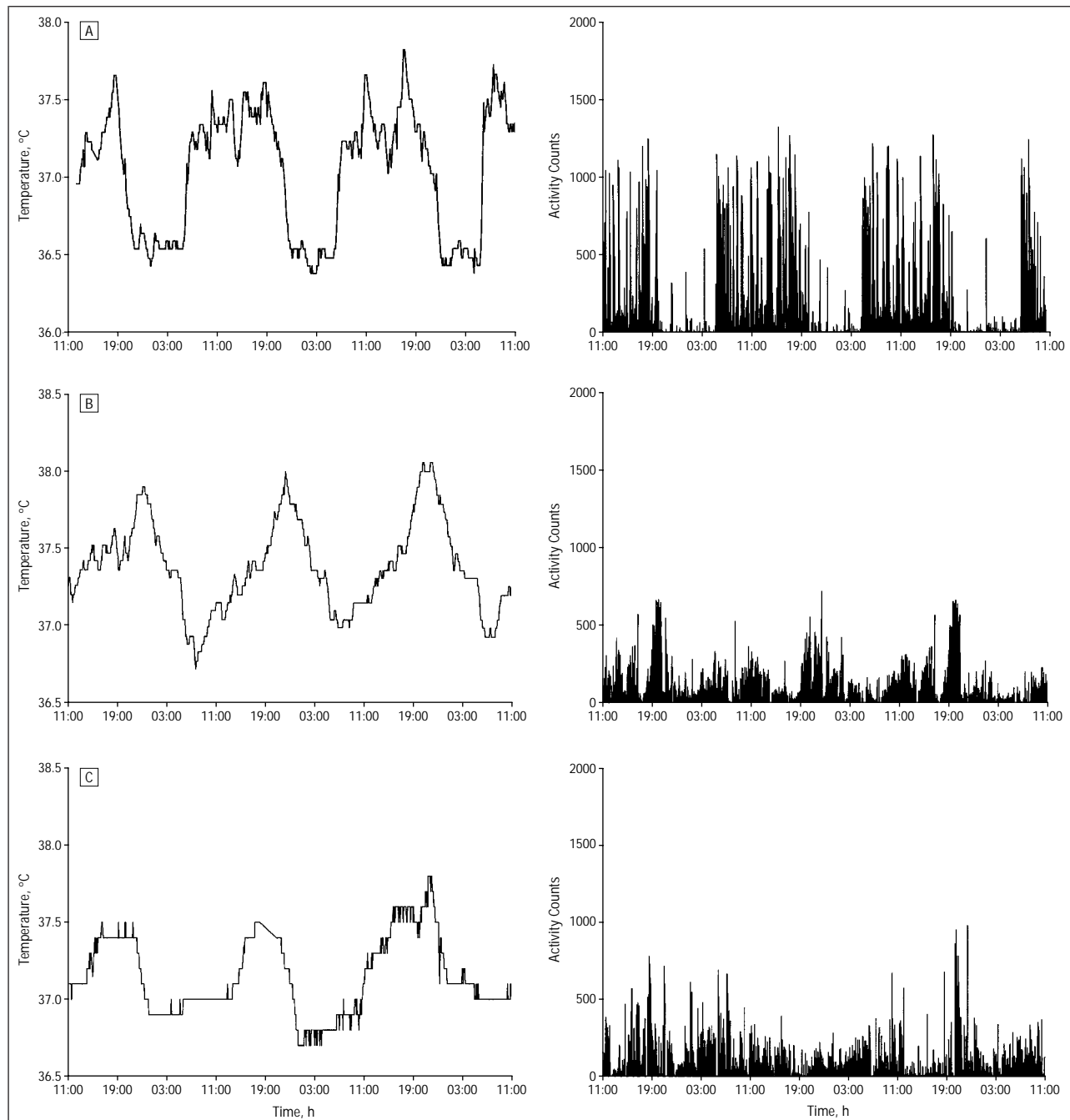
### DIAGNOSTIC COMPOSITION OF THE SAMPLE

Thirty-eight subjects underwent postmortem, neuropathological examination; 27 were given a primary diagnosis of AD, and 4 were diagnosed with both AD and DLB. One of these 4 was also diagnosed as having multi-infarction dementia. Ten patients were diagnosed as having FTD and 1 patient was diagnosed as having DLB. Of the 10 patients diagnosed as having FTD, 5 patients were

given a diagnosis of Pick disease and 5 patients were given a diagnosis of corticobasal ganglionic degeneration. One of the patients with FTD (Pick) was diagnosed as having DLB, as well. Because of the parkinsonian motoric features of DLB affecting the circadian analysis, the small number of subjects given this diagnosis, and the problems of mixed diagnosis inherent with this group, we excluded them from further study. This left 23 patients with AD, 9 patients with FTD, and 8 normal elderly subjects for analysis. There were no differences between the ages of the control ( $72.8 \pm 2.1$ ), AD ( $70.6 \pm 1.2$ ), and FTD ( $69.4 \pm 1.8$ ) groups ( $F_{2,37} = 0.45$ ,  $P = .60$ ). The age of dementia onset of the AD ( $59.9 \pm 1.3$ ) and FTD ( $62.2 \pm 2.0$ ) groups were similar ( $F_{1,30} = 0.87$ ,  $P = .40$ ), although mean  $\pm$  SD duration of illness was longer in AD ( $13.0 \pm 0.7$ ) than in the FTD ( $9.3 \pm 1.1$ ) group ( $F_{1,30} = 8.42$ ,  $P = .007$ ).

### ACTIVITY LEVELS

There were several differences in the gross activity levels of the different diagnostic groups (**Figure 2A**). Mean diurnal activity was significantly higher in AD patients than in FTD patients, although both were significantly lower than control levels ( $F_{2,35} = 11.38$ ,  $P < .001$ ). Noc-



**Figure 1.** Representative samples of activity recorded in 5-minute epochs and core-body temperature data recorded in 6-minute epochs of 3 subjects in this study. A, Representative data from a normal elderly subject. B, Representative data from a subject with Alzheimer disease. C, Representative data from a subject with frontotemporal degeneration.

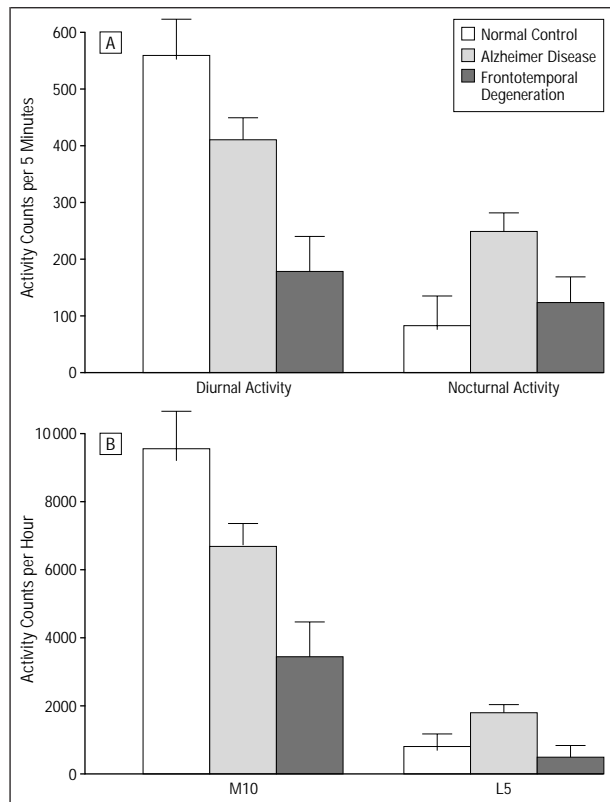
turnal activity levels were significantly higher in AD patients than in controls. The M10 and L5 results confirm the impressions from the diurnal and nocturnal activity analyses (Figure 2B). The M10 levels were significantly reduced in both dementia groups ( $F_{2,35}=9.39$ ,  $P<.001$ ), with FTD patients having lower levels than AD patients. The L5 was significantly elevated in the AD group over both FTD and controls ( $F_{2,35}=4.760$ ,  $P=.01$ ).

Interdaily stability was lower in both diagnostic groupings than in controls ( $F_{2,35}=6.13$ ,  $P=.005$ ), and there were no differences between the 2 diagnostic groups (Figure 3A). Intradaily variability (Figure 3B), how-

ever, was higher in the FTD group than in both controls and AD ( $F_{2,35}=5.39$ ,  $P=.009$ ).

#### COSINOR ANALYSES OF ACTIVITY AND TEMPERATURE RHYTHMS

Several patients showed no significant improvement in the measured goodness-of-fit of a 1 cycle per day rhythm of activity or temperature when compared with a mesor fit alone indicating that the data lacked circadian rhythmicity. One AD patient lacked a temperature rhythm, and 3 patients with AD had no significant activity rhythm.

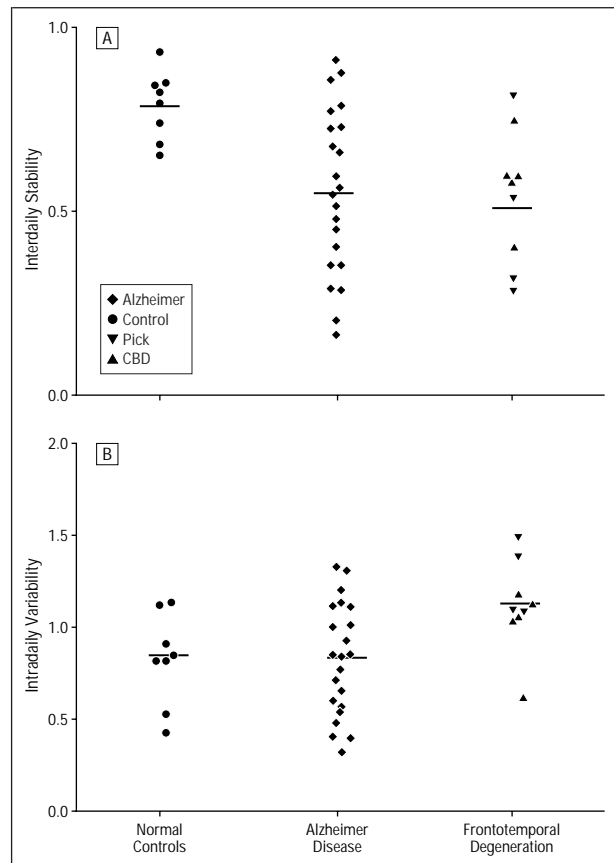


**Figure 2.** Locomotor activity (mean  $\pm$  SE) in subjects with Alzheimer disease ( $n=23$ ), frontotemporal degeneration ( $n=9$ ), and controls ( $n=8$ ). A, Diurnal and nocturnal activity. Diurnal activity is defined as activity occurring from 6 AM to midnight. Nocturnal activity is defined as activity occurring from midnight to 6 AM. B, The M10 and L5 levels. The M10 is defined as the 10 most active hours during the day, and the L5 is defined as the locomotor activity occurring during the 5 least active hours during the day. Both measurements are independent of time of day.

All FTD patients had significant temperature rhythms, although 1 FTD patient had no significant activity rhythm. The lack of circadian rhythm in activity or temperature was not specific to diagnosis ( $P > .05$ , by Fisher exact test). Activity or temperature data lacking a demonstrable circadian rhythm were excluded from further cosinor analysis, leaving the temperature rhythms of 22 AD subjects to compare with 9 FTD subjects and 8 controls. Activity rhythms of 20 AD subjects were compared with 8 FTD patients and 8 controls.

The mesor of the activity rhythm was lower in both dementia diagnoses than in the control group, as would be expected from the results of the measurements of gross motor activity (**Table 1**). The mesor in FTD patients was lower than the mesor in AD patients. Relative amplitude was similar in the 3 groups. However, the phase time (**Figure 4A**) was significantly delayed in AD and advanced in the FTD group when compared with the normal elderly group. Correlation of the data to the model was lower in the FTD group when compared with both control and AD groups (Table 1).

Cosinor analysis revealed that the mesor and amplitude of the circadian rhythm of temperature, along with the goodness-of-fit of the data to the model, were similar in the 3-group model (**Table 2**). The phase of the temperature rhythm (Figure 4B) was significantly delayed in the AD patients but not in the FTD patients.



**Figure 3.** Nonparametric measurements of circadian rhythm of activity in subjects with Alzheimer disease (AD) ( $n=23$ ), frontotemporal degeneration (FTD) ( $n=9$ ), and controls ( $n=8$ ) (corticobasal ganglionic degeneration [CBD]). A, Scatterplot of interdaily stability, a measurement of the strength of the circadian rhythm. Tukey test of AD compared with controls,  $P = .02$ ; FTD compared with controls,  $P = .03$ ; and AD compared with FTD,  $P = .94$ . B, Scatterplot of intradaily variability, a measurement of the fragmentation of the rest-activity rhythm. Tukey test of AD compared with controls,  $P = .99$ ; FTD compared with controls,  $P = .04$ ; and AD compared with FTD,  $P = .01$ .

## COMMENT

Several important differences emerge in the structure of activity and temperature rhythms in progressive, degenerative dementia when diagnosis is taken into account. Nocturnal activity is higher in AD when compared with normal elderly controls, an effect not seen in FTD. Fragmentation of the activity rhythm occurs in FTD, but not AD, as evidenced by increased intradaily variability and lowered circadian goodness-of-fit when compared with a normal elderly comparison group. The circadian rhythm of temperature is phase-delayed (the time of peak temperature is later) in AD, with a commensurate delay in the activity rhythm compared with normal elderly individuals. In FTD, the temperature phase is normal and the activity phase is advanced (time of peak activity is earlier). These results confirm the findings of previous studies,<sup>42,43</sup> in which disturbances in the expression of a normal rhythm of activity and a disturbance of the sleep-wake rhythm<sup>25,44</sup> are apparent in patients with AD and FTD.

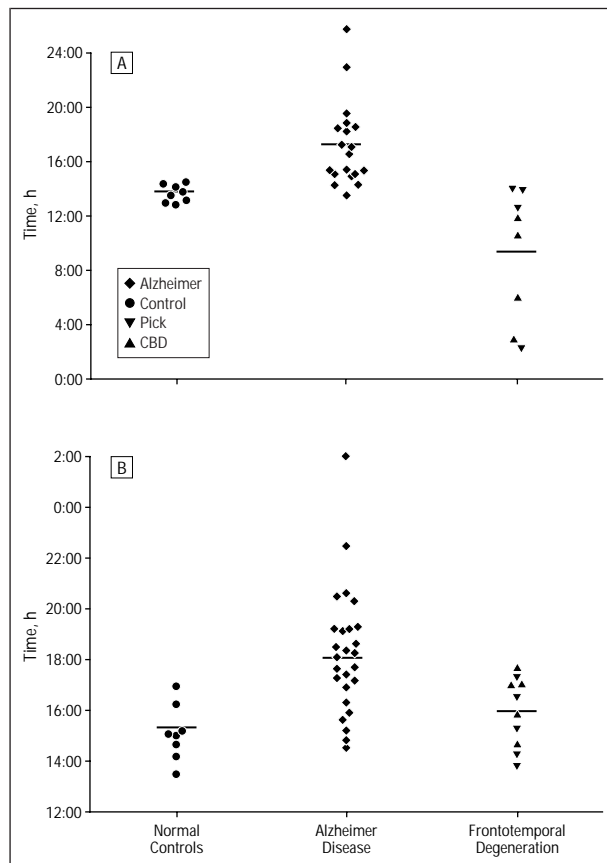
The nocturnal activity increase seen in AD in this study could be accounted for in 2 ways. The first expla-

**Table 1. Cosinor Analysis of the Activity Rhythm in Subjects With Alzheimer Disease (AD), Subjects With Frontotemporal Degeneration (FTD), and Controls**

Variable	Controls, Mean ± SD (n = 8)	AD, Mean ± SD (n = 20)	FTD, Mean ± SD (n = 8)	F (df = 2,33)	P
Mesor, counts per 5 min	438.8 ± 57.6	350.3 ± 33.2*	168.7 ± 54.3*	6.74	.004
Amplitude, counts per 5 min	302.1 ± 46.9	214.5 ± 30.5*	111.7 ± 46.9*	4.13	.02
Relative amplitude	0.69 ± 0.09	0.57 ± 0.05	0.66 ± 0.09	0.69	.50
Goodness-of-fit ( $R^2$ )	0.27 ± 0.05	0.29 ± 0.03†	0.15 ± 0.05†	3.33	.05

\*Tukey post hoc test comparison:  $P < .05$  when compared with control.

†Tukey post hoc comparison:  $P < .05$  when compared with other dementia diagnoses.



**Figure 4.** A, Acrophase of the rhythm of activity as measured by cosinor analysis in Alzheimer disease (AD) (n=20), frontotemporal degeneration (FTD) (n=8), and controls (n=8). Tukey test of AD compared with controls,  $P = .03$ ; FTD compared with controls,  $P = .04$ ; and AD compared with FTD,  $P = .0001$ . B, Acrophase of the rhythm of core-body temperature in subjects with AD (n=22), FTD (n=9), and controls (n=8). Tukey test of AD compared with controls,  $P = .003$ ; FTD compared with controls,  $P = .69$ ; and AD compared with FTD,  $P = .04$ . CBD indicates corticobasal ganglionic degeneration.

nation is that the phase-delay of the activity rhythm in AD causes actual diurnal-type activity to be phase-shifted into the defined nocturnal period. The second explanation is that the increase could be caused by an inability of AD patients to achieve normal nocturnal quiescence. The increase in the L5 in AD demonstrates that this increase in nocturnal activity cannot be entirely explained by delayed activity phase. The L5, which quantifies activity occurring during the 5 least active hours of the day, whenever they occur,<sup>6</sup> shows a

similar pattern of increase in AD as in the nocturnal activity measurement. Therefore, AD patients show a remarkable inability to achieve normal periods of quiescence at any time during the diurnal-nocturnal cycle.

The rhythm of oscillation in core-body temperature is often taken as a marker of the activity of the SCN and of the endogenous circadian pacemaker.<sup>14</sup> Measurements of phase of the circadian rhythm of core-body temperature provide information about the state of internal timekeeping relative to the environment. While our patients were not studied under true constant routine conditions in this investigation,<sup>45</sup> the recorded temperature rhythm may provide an approximation of the endogenous circadian phase in these subjects. Sleep-wake and rest-activity rhythms are influenced and often determined by the phase of the circadian pacemaker.<sup>11,13</sup> Therefore, the observed phase-delay in the rhythm of core-body temperature could be indicative of a phase-delay in output of the SCN, which is then causing the phase-delay observed in the rest-activity rhythm of our subjects with AD.

It is also possible that phase-delay in the rest-activity rhythm, perhaps caused by weakening of the sleep homeostat,<sup>23</sup> is causing phase-delay in the temperature rhythm. In this scenario, the observed core-body temperature rhythm's phase-delay is caused by additional evening and night light exposure. This additional stimulus affects the phase-delay portion of the phase-response curve to light.<sup>46</sup> This explanation is unlikely, however, since FTD patients, who have a phase-advanced activity rhythm, do not show a commensurate phase-advance in their temperature rhythm. The temperature rhythm of FTD patients is remarkable for its similarity to normal elderly, even with activity rhythms that are more disturbed than those seen in AD. Another possibility is that afternoon agitation, often observed in AD patients, could be influencing the activity and consequently the temperature rhythm. Further studies, with more control of activity, could help to elucidate the mechanism of the phase-delay seen in AD.

Frontotemporal degeneration patients, therefore, show a fundamentally different type of circadian abnormality than do AD patients. The expression of an entrained circadian rhythm, as an organized pattern of rest-activity, is compromised in FTD, even while a normal rhythm of core-body temperature is maintained, while,

**Table 2. Cosinor Analysis of the Temperature Rhythm in Subjects With Alzheimer Disease (AD), Subjects With Frontotemporal Degeneration (FTD), and Controls**

Variable	Controls, Mean $\pm$ SD (n = 8)	AD, Mean $\pm$ SD (n = 22)	FTD, Mean $\pm$ SD (n = 9)	F (df = 2,36)	P
Mesor, °C	36.91 $\pm$ 0.18	37.29 $\pm$ 0.10	37.32 $\pm$ 0.15	2.19	.10
Amplitude, °C	0.29 $\pm$ 0.07	0.44 $\pm$ 0.04	0.45 $\pm$ 0.06	1.95	.20
Goodness-of-fit ( $R^2$ )	0.34 $\pm$ 0.07	0.48 $\pm$ 0.04	0.49 $\pm$ 0.06	1.71	.20

in AD, both central pacemaker and behavioral expression are altered. Therefore, in AD, treatments that act at the level of the central pacemaker, such as light or melatonin, may be effective in treating the behavioral disturbances. Dementia patients have been noted to have abnormalities in their rhythms of melatonin secretion.<sup>47,48</sup> This dysfunction has been noted not only in patients with clinical diagnosis of AD,<sup>9</sup> but confirmed after postmortem analysis.<sup>49</sup> Light therapy, given after the temperature nadir, may also be an appropriate treatment. However, determining the precise temperature nadir before beginning any chronobiological treatment is important since it can occur very late in some subjects, sometimes later than 11 AM. If light were given before or during the time of the temperature nadir, the phase could be shifted in the direction opposite from expectation. Chronobiological treatments, aimed at the SCN and the endogenous circadian rhythm in FTD, are unlikely to be effective in treating the disrupted rest-activity rhythms of this form of dementia. In FTD, the central pacemaker seems to be functioning normally, with difficulties emerging downstream from the SCN. Further work is needed to understand the nature of the rest-activity rhythm disturbance in FTD.

One important limitation of this investigation is that only male dementia patients were studied. Women show different patterns of sleep and circadian physiology during aging than men.<sup>50-53</sup> Therefore, the present results should be interpreted cautiously regarding their generalizability to women. Another clear limitation is the advanced state of dementia in these subjects. Sleep disturbance can occur early during the course of a dementing illness.<sup>4,54</sup> Further work could clarify the contributing roles of the circadian timing system and the sleep homeostat in early dementia.<sup>55</sup> These patients also were studied without the benefit of a constant routine.<sup>56</sup> A constant routine protocol would allow for more precise quantification of endogenous circadian phase and amplitude of corebody temperature. The placement of the activity monitor on the ankle could also lead to our activity measurements being confounded by the presence of periodic leg movements of sleep, tremor, or akathisia in some of our subjects.

This study does support the hypothesis that central changes cause the observed, rhythmical changes identified previously in AD and FTD. In addition, testing circadian disturbances may be an effective way to differentially diagnose these 2 degenerative dementias. Localizing the exact nature of disturbance could lead to new treatments for these debilitating symptoms of dementia.

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