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Phenotyping Apathy in Individuals With Alzheimer Disease Using Functional Principal Component Analysis

Jamie M. Zeitzer, Ph.D., Renaud David, M.D., Leah Friedman, Ph.D., Emmanuel Mulin, M.D., René Garcia, Ph.D., Jia Wang, M.S., Jerome A. Yesavage, M.D., Philippe H. Robert, M.D., and William Shannon, Ph.D.

Department of Psychiatry and Behavioral Sciences, Stanford University (JMZ, LF, JAY) and Psychiatry Service, Veterans Affairs Palo Alto Health Care System (JMZ, LF, JAY), Palo Alto, CA; Centre Memoire de Ressources et de Recherche, CoB Tek, CHU, University of Nice Sophia Antipolis (RD, EM, PHR) and Laboratoire de Neurobiologie et Psychotraumatologie, University of Nice Sophia Antipolis (RG), Nice, France; and Department of Medicine, Washington University in Saint Louis School of Medicine (WS, JW), St Louis, MO

Abstract

Objectives—To determine if there is a specific pattern of gross motor activity associated with apathy in individuals with Alzheimer disease (AD).

Design—Examination of ad libitum 24-hour ambulatory gross motor activity patterns.

Setting—Community-dwelling, outpatient.

Participants—Ninety-two individuals with AD, 35 of whom had apathy.

Measurements—Wrist actigraphy data were collected and examined using functional principal component analysis (fPCA).

Results—Individuals with apathy have a different pattern of gross motor activity than those without apathy (first fPCA component, $p < 0.0001$, $t = 5.73$, $df = 90$, t test) such that there is a pronounced decline in early afternoon activity in those with apathy. This change in activity is independent of depression ($p = 0.68$, $F_{[1, 89]} = 0.05$, analysis of variance). The decline in activity is consistent with an increase in napping. Those with apathy also have an early wake and bedtime (second fPCA component, $t = 2.53$, $df = 90$, $p < 0.05$, t test).

Conclusions—There is a signature activity pattern in individuals with apathy and AD that is distinct from those without apathy and those with depression. Actigraphy may be a useful adjunctive measurement in the clinical diagnosis of apathy in the context of AD.

Keywords

Alzheimer disease; actigraphy; apathy; circadian; functional data analysis; sleep

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Send correspondence and reprint requests to Jamie M. Zeitzer, PhD, 3801 Miranda Avenue (151Y), Palo Alto, CA 94304. jzeitzer@stanford.edu.

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OBJECTIVE

A breakdown of the normal diurnal variation in the timing of sleep and wake is a hallmark of advanced Alzheimer disease (AD) and occurs in about half of all individuals with AD.^{1,2} Postmortem evidence indicates that this disruption of normal sleep and wake patterns may be due to degeneration of the suprachiasmatic nucleus,³ the locus of the central circadian clock in humans.^{4,5} This severe disruption in the timing and consolidation of sleep is of significant societal consequence as it is rated as one of the most important reasons that family caregivers institutionalize individuals with AD.^{6–9} There are no known prognostic indicators of which patients with AD will have a disruption of normal sleep timing.

Another common phenomenon associated with AD is apathy. *Apathy* is broadly defined as diminished motivation accompanied by a reduction in at least two of three additional areas (lack of initiative, lack of interest, emotional blunting).¹⁰ Apathy is a psychiatric disturbance that is distinct from depression,¹¹ which is important to consider as there is a strong association between depression and disruption of nocturnal sleep.¹² Through examination of focal 75-minute semistructured settings and week-long ambulatory data, we have previously reported that apathy is associated with a decrease in average motor activity during the daytime and of imputed amounts of nighttime sleep.^{13,14} These investigations relied on gross, summative measures of motor activity or imputation of sleep through examination of motor activity. How the pattern or shape of motor activity relates to the components of apathy however has not been examined. In this report, we examine the relationship between the pattern of daytime activity and components of apathy.

METHODS

Community-dwelling individuals with a diagnosis of either possible or probable AD (NINCDS-ADRDA criteria¹⁵) took part in this study (Table 1). Exclusion criteria included a history of stroke, parkinsonian symptoms, and history of head trauma with loss of consciousness. Subjects were recruited via two centers, Cohort 1 (n = 65): Nice Research Memory Center (Nice, France) and Cohort 2 (n = 27): Stanford/Veterans Affairs National Institute on Aging Alzheimer's Disease Core Center (Palo Alto, CA). We have reported previously on different actigraphy characteristics in these subjects.^{13,14} Some subjects who had been included in previous analyses were excluded from this study because of actigraphy data that was insufficient for the analyses presented here and one subject who did not have an apathy score (see later). All procedures were approved by the Comité de Protection des Personnes Sud-Méditerranée II (Nice site) and the Stanford University Institutional Review Board (Palo Alto site).

Subjects had their motor activity recorded for 1 week using an actigraph (MotionLogger, Ambulatory Monitoring, Ardsley, NY) placed on the nondominant wrist. Data were collected as the integrated movement occurring during 1-minute intervals and offloaded after the end of the 1-week collection. Caregivers for all subjects also completed the Neuropsychiatric Inventory (NPI).¹⁶ *Caregivers* were defined as individuals who were able to help in the medical and psychiatric evaluation of the subjects as well as with the completion of the sleep diaries in which the patient's daily into and out of bedtimes and naptimes were recorded. While subjects were not specifically selected for the presence of psychiatric disturbance, the presence of apathy was defined as NPI-aphathy scores greater than three (range, 0–12) and the presence of depression was defined as NPI-depression scores greater than three (range, 0–12). One subject in cohort 1 did not have NPI-depression scores available and was not included in the analyses concerning depression. Caregivers of the subjects recruited from Nice also completed the caregiver version of the Apathy Inventory (AI) (available from caregivers of 57 of 65 subjects).¹⁷

Actigraphy data were examined using two methods. Actigraphy data were analyzed using functional principal component analysis (fPCA)^{18,19} in the R programming environment.²⁰ The first continuous set of 24-hours of actigraphy data were analyzed for each subject (typically the first day). Briefly (see reference 18 for complete details), each string of 24 hours of data was fit with a nine-Fourier-based function. The equations describing these fits were subjected to fPCA that aimed at reducing the complexity of the data sets. The first four fPCA components were subjected to further analysis and comparison with measures of apathy and depression as noted in the following text.

Actigraphy data were also examined using the Cole-Kripke algorithm²¹ that is included in Action-4 software (Ambulatory Monitoring, Ardsley NY). This algorithm imputes sleep or wake on the basis of the proximal pattern of activity. The algorithm was optimized to detect wake on a background of sleep (i.e., wake during a sleep episode) but can be used to detect sleep on a background of wake (i.e., daytime napping).

Common statistical methods are noted within the text, as appropriate, and were computed with Excel (Microsoft, Redmond WA, v.11.8328.8329; *t* test, χ^2 test), OriginPro (OriginLab, Northampton MA, v.8.0.63.988; ANOVA [analysis of variance], linear regression), or SAS (SAS, Cary NC, v.9.1; stepwise regression). Data are presented as mean \pm SD unless otherwise noted.

RESULTS

Demographic variables for the French and U.S. cohorts are presented in Table 1. For analytic purposes, these two groups were combined. Individuals with and without apathy were statistically indistinguishable for age and MMSE (Mini-Mental State Examination) score, though men were, not unexpectedly,²² overrepresented in the group with apathy.

Visual inspection of the average activity curves for individuals with and without apathy uncovers obvious differences between the subject groups, the most striking of which is a larger mid-afternoon decline in activity in those with apathy (Figure 1). To determine whether this difference was consistent among individuals as well as statistically significant, we examined these data with fPCA. The first four functions uncovered by fPCA of the actigraphy data of all subjects explained 80.6% of the variance in the actigraphy data (Figure 2). Examination of the first functional principal component score (fPCA1) indicated a highly significant difference between those with and without apathy ($p < 0.0001$, $t = 5.73$, $df = 90$, *t* test). This is borne out by visual examination of the fPCA1 curves of individual subjects (Figure 3), in which there is clear separation of the curves of individuals with and without apathy. Those with apathy appear to have a smaller rise of activity at wake time, an overall lower amount of activity, and a greater midday dip in activity, as compared to those without apathy. Manual stepwise regression indicated that there was no effect of age, sex, MMSE score, or their interactions with fPCA1 scores. Furthermore, a separate two-way ANOVA examining the relationship between the presence of apathy and depression indicates that while fPCA1 scores are significantly different in those with apathy ($p < 0.0001$, $F_{[1, 89]} = 23.1$), there is no impact of the presence of depression ($p = 0.68$, $F_{[1, 89]} = 0.05$) nor an interaction between depression and apathy ($p = 0.87$, $F_{[1, 89]} = 0.85$).

To determine whether this midday dip might represent an increase in napping, on the day that was analyzed with fPCA, we examined this midday interval of 12:30–15:30 in each subject and scored each minute of actigraphy data as “sleep” or “wake” (see Methods). Individuals with apathy had significantly more quiescent periods during this 3-hour period and spent more time in relative inactivity (Table 2). Given the variety of possible definitions for what constitutes a “nap,” we examined different lengths of inactive time as minimum

criteria for considering periods of inactivity as a nap. Applying each of three different criteria, during the midday interval there was significantly more “napping” in those with apathy (Table 2).

Comparison of fPCA scores for the second component (fPCA2) indicated that there was a significant effect of apathy ($p < 0.05$, $t = 2.53$, $df = 90$, t test) (Figure 4). Visual inspection of the individual curves (Figure 4) indicates that individuals with apathy have an earlier onset and offset of activity than those without apathy. There was no effect of depression ($p = 0.57$, $F_{[1, 89]} = 0.33$, ANOVA) nor an interaction between depression and apathy ($p = 0.46$, $F_{[1, 89]} = 0.54$, ANOVA) on fPCA2 scores.

There were no significant differences in the third ($p = 0.46$, $t = 0.74$, $df = 90$, t test) or fourth ($p = 0.27$, $t = 1.1$, $df = 90$, t test) fPCA components when compared between those with and without apathy.

Given the significant association of fPCA1 and fPCA2 scores with apathy in individuals with AD, we performed a receiver operating characteristic (ROC) analysis on these data (software available at <http://www.stanford.edu/~yesavage/ROC.html>).²³ We first performed ROC on fPCA1 scores alone and assumed equal weighting for sensitivity and specificity. This analysis indicated that using a cut-point of -379.42 in fPCA1 scores ($\chi^2 = 29.5$, $df = 91$, $p < 0.001$) yields a sensitivity of 0.60 and a specificity of 0.92. Including both fPCA1 and fPCA2 scores yielded two cut-points, the first being -379.42 for fPCA1 scores and the second being 309.14 for fPCA2 scores ($\chi^2 = 8.53$, $df = 91$, $p < 0.01$). The category of “no apathy” comprised individuals who had fPCA1 scores less than -379.42 and individuals who had fPCA1 scores greater than -379.42 but fPCA2 scores greater than 309.14. The category of “apathy” was composed of individuals who had fPCA1 scores greater than -379.42 and fPCA2 scores less than 309.14. Using both fPCA1 and fPCA2 scores, the sensitivity was 0.85 and the specificity was 0.80.

To examine whether a particular aspect of apathy best correlated with differences in motor activity patterns, we compared fPCA1 and fPCA2 scores with the three subcategories of the AI (Cohort 1 only). As expected, the total AI score was significantly correlated with fPCA1 scores ($p < 0.001$, $R^2 = 0.33$, $F_{[1, 55]} = 29.2$, linear regression). The fPCA1 scores were similarly well correlated with the emotional blunting ($p < 0.001$, $R^2 = 0.29$, $F_{[1, 53]} = 23.5$, linear regression), loss of initiative ($p < 0.001$, $R^2 = 0.27$, $F_{[1, 53]} = 21.2$, linear regression), and loss of interest ($p < 0.001$, $R^2 = 0.25$, $F_{[1, 53]} = 19.0$, linear regression) subscales of the AI. The relationship was such that the greater the apathy or apathy component emotional blunting, the higher the fPCA1 score (greater dip in midday activity).

Neither the total AI score nor any of the three subscales were significantly correlated with fPCA2 score (p 's > 0.13 , $R^2 < 0.03$, $F_{s[1, 53]} < 2.42$ for AI subscales and $F_{[1, 55]} = 2.18$ for AI total; linear regression).

CONCLUSIONS

These data exhibit the first significant differences that have been described in the activity patterns of individuals using the fPCA technique. Our analyses show that the primary change in daytime motor activity in individuals with apathy and AD, as opposed to those with AD and no apathy, is a significant decline in mid-afternoon activity that is likely representative of an increase in napping. In individuals with apathy, the morning rise and the evening decline in activity levels are also shifted to a slightly earlier hour. Furthermore, our data confirm our previous finding that there is an overall decline in daytime activity levels in individuals with apathy.¹³

The symptomatology of depression and apathy has considerable overlap, including the presence of sleep disruption.^{12,14} Our data, however, indicate that there is a unique pattern of daytime activity in those with AD and apathy that is not affected by the presence of depressive symptoms. At least in how it relates to motor activity patterns, our data support the contention that depression and apathy are distinct clinical entities¹¹ and that actigraphy may be a useful tool in discriminating apathy from depression. One important limitation is that while all subjects were on stable doses of medications, notably ones that act on the cholinergic system, differences in other drugs were not noted and could affect locomotor activity patterns if differentially distributed in the population.

The finding that there is a specific decline in mid-afternoon activity is consistent with a novel hypothesis—the decline in circadian amplitude in AD may occur specifically in individuals with apathy. Wakefulness in humans is typically consolidated into a single daily period lasting approximately 16 hours. This wake-consolidation process can be explained as the interaction between two systems—the circadian clock and a sleep/wake homeostat.²⁴ Homeostatic pressure for sleep increases with time spent awake, but this pressure is offset by a gradually increasing circadian drive for wake that peaks just before normal bedtime. Mid-afternoon is a weak spot in the wake-consolidation process because the circadian drive for wake is not yet at its peak, but there is enough accumulated homeostatic pressure for sleep (napping) to occur. Culturally, this often manifests as a siesta. In individuals with AD and apathy, the tendency to sleep during the mid-afternoon appears to be significantly greater than individuals with AD but without apathy. This mid-afternoon napping along with the earlier decline in activity (see Figures 1 and 4) may reflect a decline in circadian wake drive, possibly due to lower circadian amplitude secondary to suprachiasmatic nucleus cell loss, specifically in AD patients with apathy. Future research that examines postmortem tissue will be dispositive in examining this hypothesis.

Using actigraphy, we found that individuals with AD and apathy had a signature activity profile that was quite dramatically different from that found in individuals with AD who did not have apathy. The fPCA analysis of the actigraphy data yielded an 85% sensitivity and 80% specificity in identifying those individuals with AD who had NPI-defined apathy. Given the clear differentiation of the activity patterns of those with and without apathy, actigraphy could be a useful adjunctive tool in the diagnosis of ambiguous cases of apathy and to differentiate apathy from depression in those with AD.

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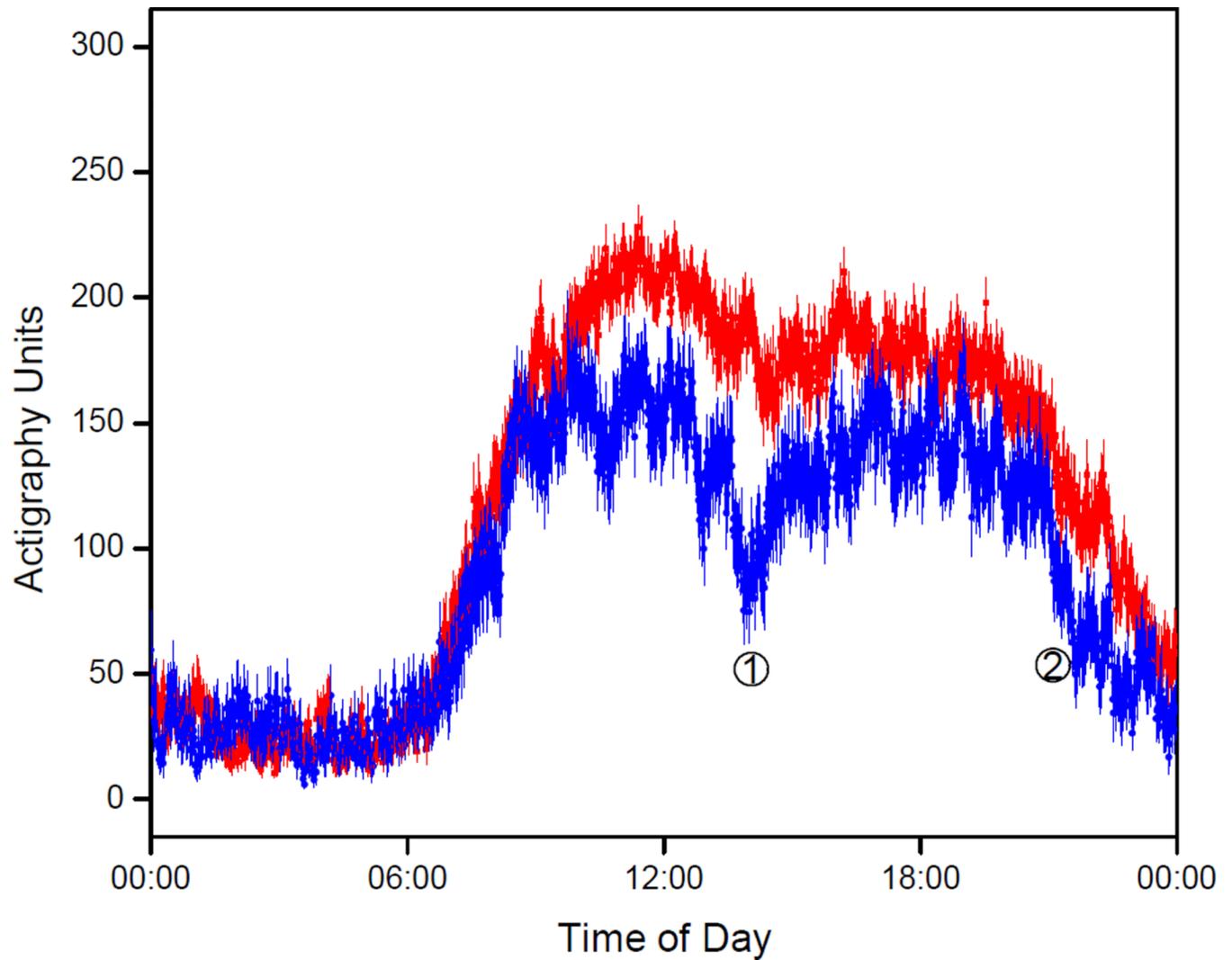


FIGURE 1.

Average activity curves in individuals with AD and with (blue) or without (red) apathy. Data were averaged at each minute across subjects and are presented \pm SEM. The encircled 1 notes the dip in midday activity that appears larger in those with apathy, which is substantiated by the fPCA analysis (fPCA1, see text). The encircled 2 notes an earlier offset in activity in those with apathy, which is substantiated by the fPCA analysis (fPCA2, see text).

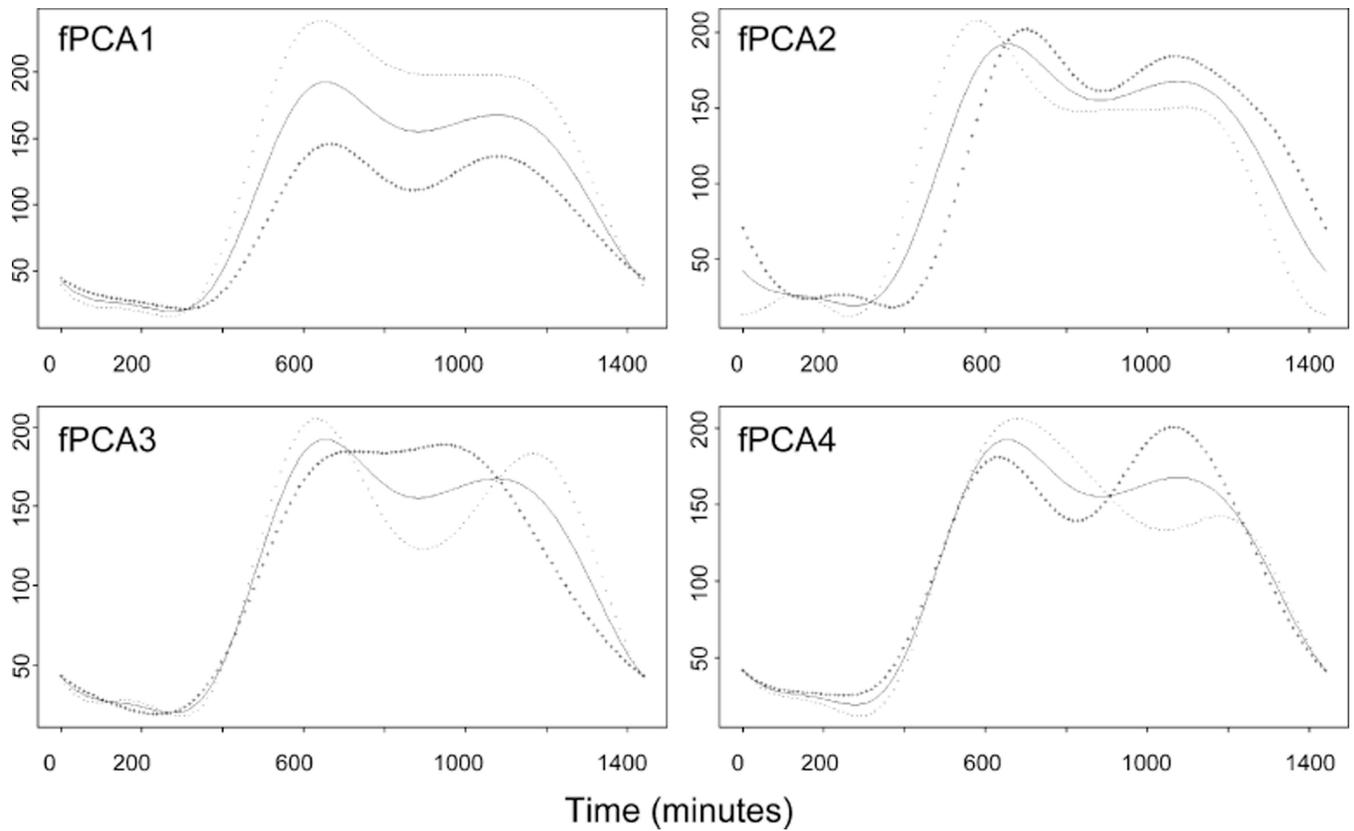


FIGURE 2.

Results of the fPCA analysis. The solid curve in each of the four plots is the same average curve. Adding (+) or subtracting (–) each of the first four components derived from the fPCA analysis are shown separately in the four plots. All subjects are represented in these curves independent of diagnosis of apathy.

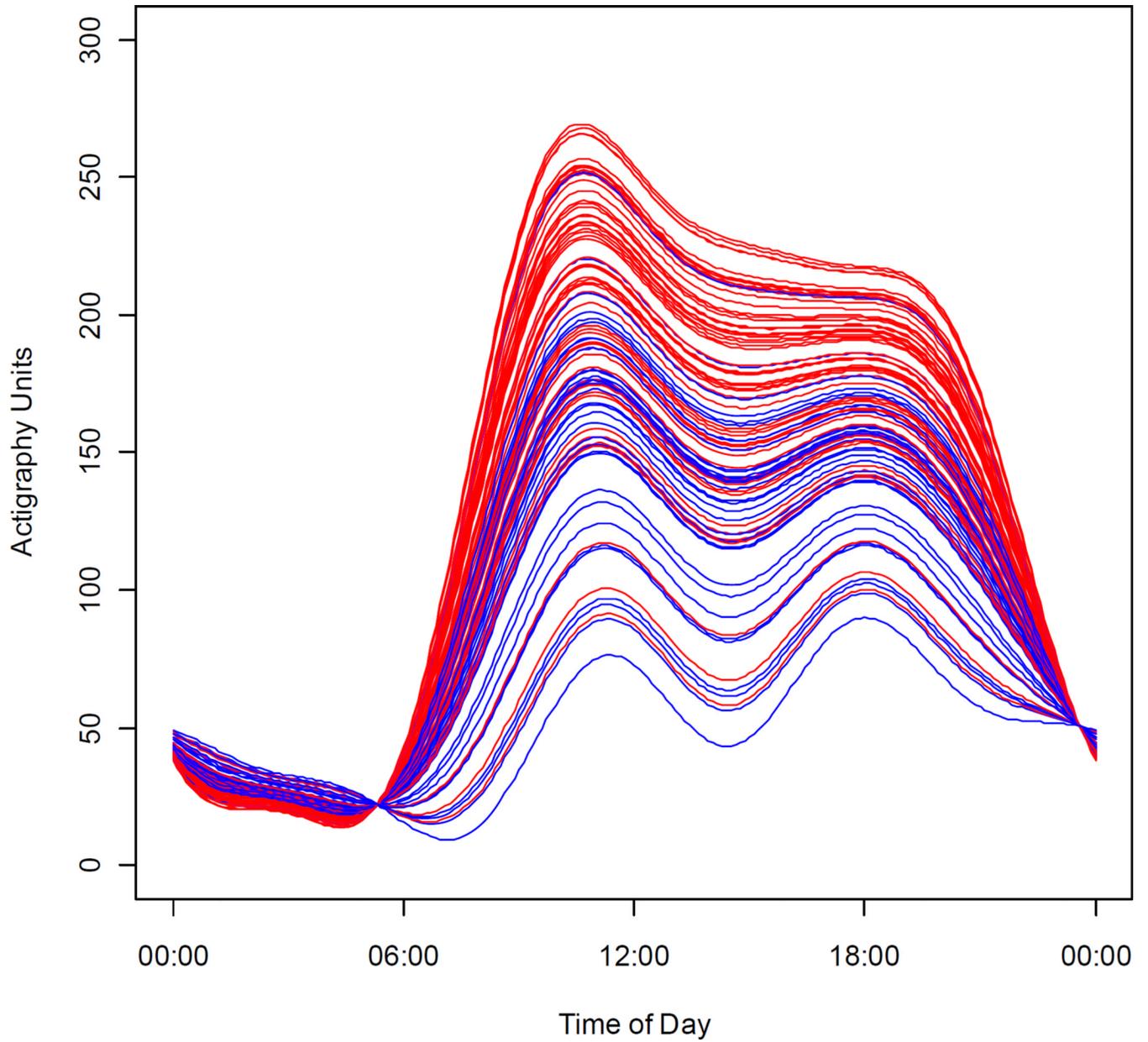


FIGURE 3.
fPCA1 curves for individual subjects with (blue) and without (red) apathy.

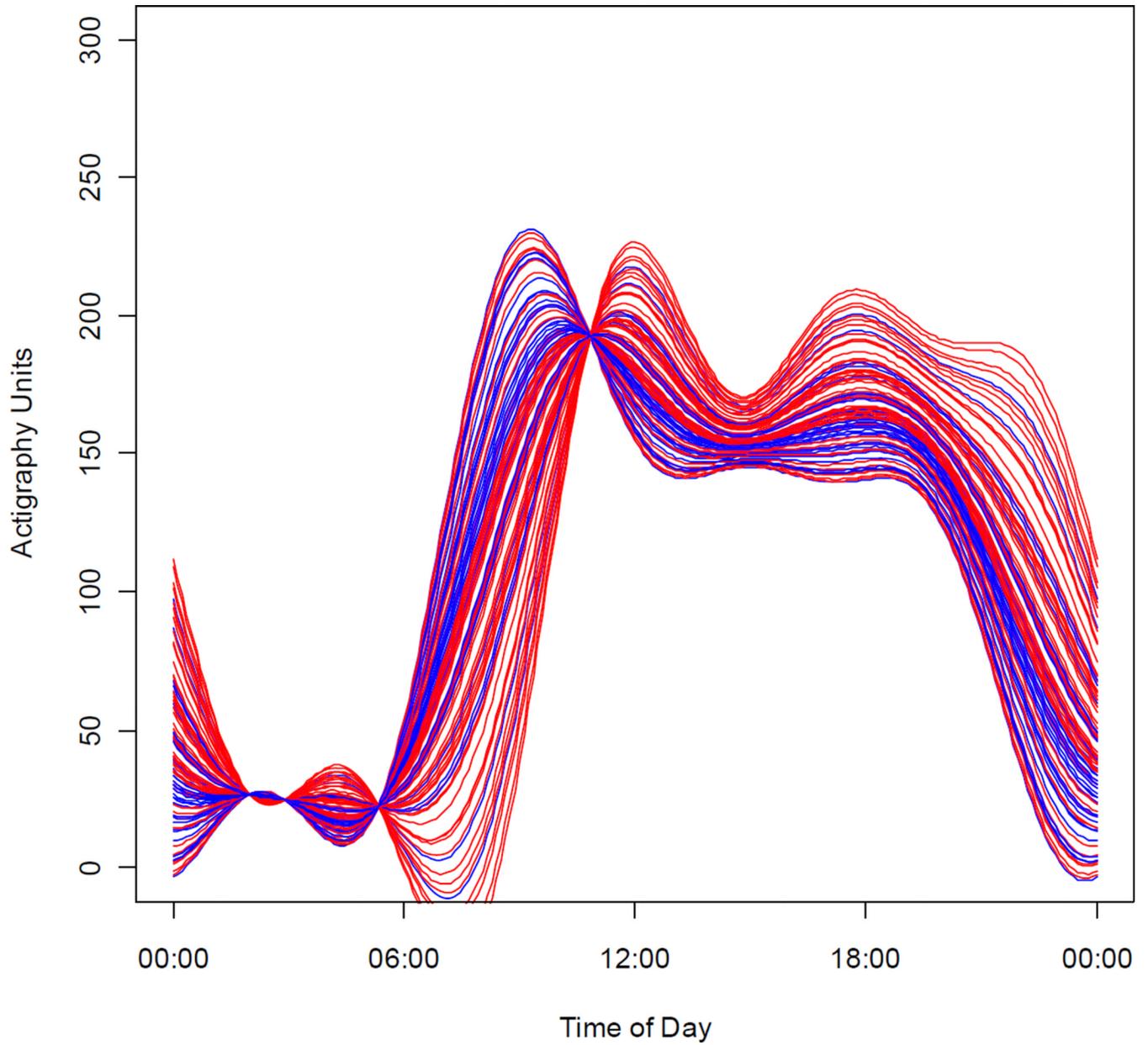


FIGURE 4.
fPCA2 curves for individual subjects with (blue) and without (red) apathy.

TABLE 1

Characteristics of AD Participants With and Without Apathy in Both Cohorts

	Cohort 1 (France) (n = 65)		Cohort 2 (U.S.) (n = 27)		Combined (n = 92)	
	Apathy	No Apathy	Apathy	No Apathy	Apathy	No Apathy
Sex (♀/♂)	10/15	26/14 ^a	1/9	9/8 ^a	11/24	35/22 ^a
Age, years	78.4 ± 4.75	76.8 ± 7.35	82.6 ± 3.81	77.3 ± 7.68	79.6 ± 4.84	76.9 ± 7.39
MMSE	20.8 ± 5.14	21.2 ± 4.79	20.7 ± 4.42	21.4 ± 8.12	20.8 ± 4.87	21.2 ± 5.90

Notes:

^a p < 0.05 apathy versus no apathy, df = 1, $\chi^2 = 7.8$, χ^2 test.

TABLE 2

Napping 12:30–15:30 in Those With and Without Apathy

	Apathy	No Apathy
Number of naps	1.62 ± 1.35	0.69 ± 1.14 ^a
Time (minute) spent in naps, T = 1 minute	41.3 ± 39.9	17.3 ± 29.7 ^a
Time (minute) spent in naps, T = 5 minutes	39.1 ± 39.77	15.9 ± 29.1 ^a
Time (minute) spent in naps, T = 10 minutes	35.9 ± 38.6	14.8 ± 28.4 ^a

Notes: Discrete nap bouts were separated by at least 5 minutes of wake. The T-threshold is the number of consecutive minutes of “sleep” that were necessary before a stretch of time was determined to be a nap.

^a $p < 0.01$, t s < -3.09 , $df = 95$, t test.