Characterizing Sleep-Wake Circadian Rhythm Consolidation in Early Childhood and Its Association with Motor Development Using Actigraphy

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Abstract

Study Objective: Actigraphy has been widely used in clinical studies to study sleep-activity patterns, but the analysis remains the major obstacle for researchers. This study proposed a novel method to characterize sleep-wake circadian rhythm using actigraphy and further used it to describe early childhood daily rhythm formation and examine its association with physical development.

Methods: We developed a machine learning-based Penalized Multi-band Learning (PML) algorithm to sequentially infer dominant periodicities based on Fast Fourier Transform (FFT) and further characterize daily rhythms. We implemented and applied the algorithm to Actiwatch data collected from a 262 healthy infant cohort at 6-, 12-, 18-, and 24-month old, with 159, 101, 111, and 141 subjects participating at each time point respectively. Autocorrelation analysis and Fisher's test for harmonic analysis with Bonferroni correction were applied to compare with PML. The association between activity rhythm features and early childhood motor development, assessed by Peabody Developmental Motor Scales-Second Edition (PDMS-2), was studied through linear regression.

Results: PML results showed that 1-day periodicity is most dominant at 6 and 12 months, whereas 1-day, 1/3-day, and 1/2-day periodicities are most dominant at 18 and 24 months. These periodicities are all significant in Fisher's test, with 1/4-day periodicity also significant at 12 months. Autocorrelation effectively detected 1-day periodicity but not others. At 6 months, PDMS-2 is associated with assessment seasons. At 12 months, PDMS-2 is associated with seasons and FFT signals at 1/3-day periodicity ($p<0.001$) and 1/2-day periodicity ($p=0.039$). In particular, subcategories of stationary, locomotion, and gross motor are associated with FFT signals at 1/3-day periodicity ($p<0.001$).

Conclusions: The proposed PML algorithm can effectively conduct circadian rhythm analysis using actigraphy and characterize sleep-wake rhythm development of the early childhood population. Furthermore, our study found the association between daily rhythm formation and motor development during early childhood.

Keywords: circadian rhythms, actigraphy, statistical analysis, Fourier transform, early childhood development, pediatrics

Introduction

Circadian rhythms are endogenous and entrainable biological processes that follow a period of approximately 24 hours, and many physiological phenomena such as sleep-wake patterns, body temperature, and hormone levels all exhibit circadian rhythms. For humans, most circadian rhythms are under the control of the pacemaker located in the suprachiasmatic nuclei (SCN) in the anterior hypothalamus of the central nervous system, and SCN accepts environmental information such as the light/dark cycle to adjust the 24-hour cycle.[1] However, 24-hour human circadian rhythms are not mature at birth, when the predominant rhythm is ultradian, and the circadian rhythms of sleep-wake cycles and body temperature gradually develop during the first year after birth.[1-4] Many studies have investigated how circadian rhythms develop through childhood into adolescence and adults, and how they are related to health issues such as sleep problems, mental problems, and disease risks, just to name a few.[3, 5-9] It is noteworthy that the development of circadian rhythms during early childhood is associated with disease risk factors and can affect both childhood and adult life.[3] Therefore, it is important to conduct circadian rhythm studies focused on the infant population to get a thorough understanding of the formation and consolidation of daily activity rhythms during early development. While previous studies have focused on the association of circadian rhythms with obesity and other medical conditions, few have studied the association between circadian rhythms and normal physical growth.[10,11] Details in the development and consolidation of circadian rhythms during early childhood remain to be studied and how circadian rhythms relate to early childhood development shall be investigated further.[5,10,11]

This study aims to characterize the consolidation of sleep-wake rhythms during early childhood and further study its association with physical development. The sleep-wake circadian rhythm is an important aspect of circadian studies, and sleep logs, polysomnography (PSG), and actigraphy

are often used in such studies. Sleep logs are recorded manually to collect daily sleep information, but they have some inherent limitations such as subjectivity, bias, difficulty in completion by young children, and extra manual work for caregivers. PSG, as the "gold standard" in sleep studies, does not have the same issues as sleep logs, but it might be limited by high costs, in-lab setting, intrusive measures, and difficulty in long-time monitoring. Alternatively, actigraphy has become increasing used to study sleep-activity patterns as it can provide continuous and objective activity monitoring and it is low-cost and easy to wear. Actigraphy has also been validated to provide reliable information on sleep and circadian rhythms.[11] However, the analysis of time series data from actigraphy remains the major obstacle for researchers. Current major statistical methods, either parametric based on cosinor analysis or nonparametric,[12-17] are not specifically suitable for young infant and toddler populations, whose sleep-wake rhythms are not mature and not sinusoidal.[1-5, 7] Therefore, traditional approaches targeting adult daily rhythms might not work, as detailed infant activity rhythms cannot be captured. There is a need to develop appropriate methodology to study activity patterns of infant and toddler populations and better characterize the formation of sleep-wake rhythms during early childhood.

Here we propose a Penalized Multi-band Learning (PML) approach that can complement current circadian rhythm analysis to characterize daily sleep-activity rhythms based on periodic information in actigraphy. PML extracts periodic information using Fast Fourier Transform (FFT) and then performs penalized selection based on regularization, a classic approach used in machine learning, to identify dominant periodicities and further characterize daily activity rhythms.[18, 19] Using the proposed method, we characterized the formation and consolidation of infant sleep-activity circadian rhythms and further studied its association with physical development during early childhood.

Methods

Data

The study subjects are from a 262 healthy newborn cohort recruited in 2012-2013 by Shanghai Children's Medical Center, Shanghai, China. Actiwatch data were collected at 6, 12, 18, and 24 months old, with 159, 101, 111, and 141 subjects at each time point respectively, and not all subjects from the cohort participated each time. Infants and toddlers were required to wear Actiwatch-2 (Phillips Respironics Mini-Mitter) on the ankle for seven consecutive days. Wearing on the ankle is commonly recommended for young infants/toddlers.[20] The Actiwatch-2 utilizes a piezoelectric sensor to detect accelerations between 0.5 and 2.0g with a frequency response range between 0.35-7.5Hz, and activity counts summarize accelerations over each epoch. The data output format for Actiwatch-2 was configured to be activity count per 1-minute epoch. Based on sleep diaries and activity plots for each individual, non-wear periods showing straight lines of zero activity counts were removed. Non-wear periods can be differentiated from sedentary behaviors or sleep as the former gives almost all zeros while the latter gives non-zero activity counts every now and then. Figure 1 shows the activity plots for subject ID 17, and it can be seen that at 6 months, low and high activities are intermittent during the day, suggesting multiple daytime naps, while near-zero activity levels at night suggests long nighttime sleep. At 12 months, three activity peaks, one morning nap and one afternoon nap can be identified. Then at 18 and 24 months, two activity peaks formed and stabilized, showing one afternoon nap only. The daily activity rhythm developed and stabilized as the infant grew. In addition to Actiwatch data, demographic information and family information were collected at baseline, such as child sex, child birthdate, parental age, child birth weight and body length, parents' heights and weights, parental educational levels and working statuses, and family income. Peabody Developmental Motor Scales-Second

Edition (PDMS-2) were used to assess early childhood physical development at 6, 12, 18, and 24 months.[21] The institutional review board of the Shanghai Children's Medical Center, Shanghai Jiao Tong University approved the study and the approval number is SCMCIRB-2012033. Parents of children who participated in the study all gave written informed consent.

(Figure 1 goes here)

Algorithm Overview

To describe the consolidation of sleep-activity rhythms during early childhood, we utilize periodic information to characterize daily rhythms. Specifically, we use Fast Fourier Transform (FFT) to convert time-domain signals into frequency-domain spectrum in order to extract periodic information. Figure 2 shows FFT results for ID 17 at each age respectively. 1-day periodicity is most dominant at all time points. 1/5-day and 1/4-day periodicities can be identified at 12 months. 1/2-day and 1/3-day periodicities did not become dominant until 18 and 24 months. It is noteworthy that each periodicity is not interpreted alone but combined to understand the overall pattern. As suggested on the right panel of Figure 2, the combined 1/5-day and 1/4-day periodicities form the three-peak two-nap pattern at 12 months. Likewise, the combined 1/2-day and 1/3-day periodicities exhibit the two-peak one-nap pattern at 18 and 24 months. Therefore, the combination of dominant periodicities can be utilized to capture main sleep-activity patterns at each age and describe the gradual consolidation of daily rhythms in early childhood development.

(Figure 2 goes here)

A simplified procedure of the PML algorithm is presented here, and details can be found in Supplementary Materials. Let X be an n by p matrix, where n denotes the number of individual observations, and p (lowercase p) denotes the number of periodicities from FFT. Let Θ be a p by

p diagonal matrix, with each diagonal element $0 \leq \theta_{j,j} \leq 1, j = 1, \ldots, p$. Θ identifies columns of dominant periodicities from X in the way that dominant periodicities corresponding to nonzero $\theta_{j,j}'s$ are selected.

In order to estimate Θ and identify dominant periodicities, we use a penalized selection method similar to Lasso, a widely used method in shrinkage and selection of a subset of features in regression models and machine learning approaches.[19] In regression, Lasso penalty is most effective in selecting a few important features while suppressing regression coefficients of other non-selected features to 0.[19] In our case, Lasso penalty serves to select a few dominant periodicities through diagonal elements of Θ instead of regression coefficients. (Supplementary Materials)

λ is a tuning parameter for the penalty term, and by setting λ large enough, all diagonal elements of Θ, namely all $\theta_{j,j}'s$, are suppressed to zero and no periodicities are selected. As λ decreases, some $\theta_{j,j}'s$ become nonzero and they correspond to the most dominant periodicities that shall be selected sequentially according to how dominant they are. We use mean squared error (MSE) as the criterion for choosing λ and the number of nonzero $\theta_{j,j}'s$ (the number of dominant periodicities selected) as well as evaluating how much variability is not explained by the selected periodicities. By decreasing λ, we identify dominant periodicities sequentially and characterize the daily sleep-activity rhythm at each age. An R package named PML has been developed (https://CRAN.R-project.org/package=PML) for the implementation of the PML algorithm.[22]

To rigorously conduct statistical tests and select significant periodicities, we apply Fisher's Test for Harmonic Analysis.[23] It is a sequential test for ordered statistics, and periodicities are first ordered and then tested for significance. If one periodicity is statistically significant, the next one will be tested further. If not, the sequential test will stop. At each step, the critical value at which

to declare statistical significance is different. In some publications the method may not be implemented correctly so we included the sequential test in the R package for easy implementation. Because we are performing multiple testing, Bonferroni correction is used to adjust p-values. If we conduct the tests at significance level α, we will reject the null hypothesis if p-value $\leq \alpha/p$, where p is the number of periodicities, and conclude that the periodicity is significant.

To evaluate the effectiveness of the PML algorithm, we compare it with the standard approach autocorrelation. Autocorrelation r_k is calculated between activity measurements with a time lag k, and the coefficient r_{24} for a 24-hour time lag is of primary interest in circadian studies.[24] r_k ranges between -1 and 1, and a k-hour periodic pattern can show a higher value of correlation coefficient r_k. In the plot of r_k against the time lag k, a peak around k=24 can be observed when there is a dominant circadian pattern of 24-hour periodicity. We plot autocorrelation against the time lag to compare the autocorrelation method with our algorithm.

We further conduct linear regression to study the association between the consolidation of daily activity rhythms and early childhood physical development. PDMS-2 is considered as early childhood developmental assessment and used as the outcome. If PDMS-2 total motor standard scores are found to be associated with daily rhythm features, the standard scores for subtests including stationary, locomotor, object manipulation, grasping and visual motor integration as well as gross motor and fine motor are used as the outcome to further examine which specific subcategory is associated. Gross motor represents the overall performance on stationary, locomotion and reflexes (6 months) or object manipulation (12, 18, 24 months) for infants, and fine motor represents the overall performance on grasping and visual-motor integration.

The FFT signals at dominant periodicities identified by PML are used as daily rhythm features and considered as covariates in the model. In addition to periodic features, demographic information and family information as potential confounders are also considered in the model. Backward selection is used in the model fitting process. While some variable (denoted as variable A here) may appear to be statistically significant in the complete model, after removal of insignificant variables in the variable selection process, variable A may become insignificant. In such cases, variable A will also be removed in the final model to achieve parsimony.

Linear regression is conducted at 6, 12, 18, 24 months respectively to study the association between daily rhythms and motor development. For final model comparison, r^2 that measures the proportion of the variation in the outcome explained by the model and also the adjusted r^2 that modifies r^2 based on the number of predictor variables were also calculated. All statistical analyses were conducted in R (Version 3.3.2).

Results

Identification of Dominant Periodicities by PML

As shown in Figure 3, at each age, we plot MSE against the number of nonzero θ's, and specifically, we only plot the points where the number of nonzero θ's (periodicities selected) increases as the penalty λ decreases. For 6 months and 12 months, the first harmonic at 1-day is most dominant, as we can observe a large dip in MSE when the first periodicity is selected while the following periodicities that are further selected do not cause the same level of decrease. For 18 and 24 months, the first three periodicities of 1-day, 1/3-day, 1/2-day are most dominant, as selecting the first three can lead to relatively large decrease in MSE. The results indicate that during the first year, only 1-day periodicity is formed and stabilized in the infant population. Not until 18 months is the sleep-

activity rhythm stabilized, showing the pattern of one nighttime sleep, one daytime nap, and two daytime activity peaks.

(Figure 3 goes here)

Fisher's tests give similar results. As shown in Table 1, only 1-day periodicity is significant at 6 months (p-value < 10^{-5}), because for infants at this stage, sleep-activity patterns have already adjusted to a 24-hour cycle. However, daytime activities have not been stabilized yet and variations exist across days. Then at 12 months, four periodicities are significant (p-values < 10^{-5}). It is because infants' sleep-activity patterns start to stabilize, but there are variations across individuals: some take one nap in the afternoon while others take two naps, one in the morning and one in the afternoon. The one-nap pattern can be captured by the 1/3-day periodicity, while the two-nap pattern can be captured by the 1/4-day periodicity, as previously shown in Figure 2. Further, at 18 and 24 months, three periodicities are significant (p-value < 10^{-5}): 1-day, 1/2-day and 1/3-day, indicating the final consolidation of daily sleep-activity rhythms with only one daytime nap in the afternoon. In addition, the proportions of variance explained by the 1/2-day and 1/3-day periodicities increased compared to previous ages.

(Table 1 goes here.)

Comparison with Autocorrelation

To compare the PML algorithm with autocorrelation, the plot of correlation estimates against time lags is shown in Figure 4. The circadian rhythm at 24 hours can be observed at all time points, as the peaks of estimated correlation are at time lags between 23.8 hours to 24.3 hours. We can also observe some local maximal correlation estimates at other time lags: 3.3 hours at 6 months, 4.7 and 10.7 hours at 12 months, 7.5 hours at 18 months, and 7.5 and 16.3 hours at 24 months. While

3.3 hours at 6 months may seem reasonable because of the infant feeding schedule, other cycles are hard to explain.[25, 26] Autocorrelation estimates can be biased due to the presence of multiple periodicities, and generally researchers use it to verify the most dominant periodicity such as 24 hours. Thus from the autocorrelation plots, the most dominant 24-hour rhythm that yields the global maximal correlation estimate can be identified at each age, and this dominant periodicity was also identified by PML.

(Figure 4 goes here.)

Association with Motor Development

Summary of the PDMS-2 standard scores for each category are provided in Supplementary Materials (Table S1) for reference. As shown in Table 2, at 6 months, the PDMS-2 total motor scores are found to be associated with assessment seasons (p-value < 0.001). Infants receiving the PDMS-2 assessment in winter and spring tend to have lower PDMS-2 total motor scores compared to those assessed in summer and autumn. At 12 months, the PDMS-2 total motor scores are associated with both seasons and FFT signals: infants assessed in summer tend to have higher PDMS-2 total motor scores, and infants with higher FFT signals detected at 1/3-day and 1/2-day periodicities also tend to have higher PDMS-2 total motor scores (p-value < 0.001 and p-value=0.04 respectively). r^2 is 0.25 and the adjusted r^2 is 0.21. At 18 and 24 months, no association is identified between the PDMS-2 total motor scores and any other variables. The complete models before variable selection are shown in Supplementary Table S2. It is noteworthy that at 12 months, if 1-day periodicity is put in the model alone, it is also statistically significant with p-value <0.001 and r^2 and the adjusted r^2 are 0.17 and 0.15 respectively. Further adding 1/3-day and 1/2-day periodicities will make 1-day periodicity insignificant and also lead to significant increase in r^2 and the adjusted r^2 (Supplementary Table S2). It is likely because individuals

whose sleep-activity patterns are more consolidated and strongly rhythmic tend to have stronger signals at 1/3-day and 1/2-day periodicities as well as 1-day periodicity. In the final model we choose the most parsimonious one that include only 1/3-day and 1/2-day periodicities and yield highest r^2 and the adjusted r^2 (Table 2).

(Table 2 goes here.)

Because PDMS-2 total motor scores are associated with FFT signals at 12 months, further linear regression between each subtest scores and FFT signals are also examined. As shown in Table 3, subtests for stationary and locomotion as well as gross motor and fine motor are found to be associated with the 1/3-day periodicity. Gross motor represents the overall performance on the three subtests of stationary, locomotion and object manipulation for infants at 12 months, and since the association of FFT signals at 1/3-day periodicity with stationary and locomotion subtests is strong, it is expected that the association of that with gross motor is also strong. r^2 and the adjusted r^2 are 0.05 and 0.04 for the stationary model, 0.23 and 0.20 for the locomotion model, 0.21 and 0.17 for the gross motor model, and 0.15 and 0.11 for the fine motor model respectively. The complete models before variable selection are shown in Supplementary Table S3.

(Table 3 goes here.)

Discussion

Method Evaluation

The PML approach is very effective in studying daily activity rhythms among infants and toddlers. At 6 and 12 months, the dominant 1-day periodicity suggests the formation of the 24-hour cycle. At 18 and 24 months, the combination of the dominant 1-day, 1/3-day, and 1/2-day periodicities forms the consolidated daily activity pattern with two activity peaks during the day and one

afternoon nap. PML not only effectively identified population-level dominant periodicities but also characterized sleep-activity patterns without complex functional analysis. PML can complement current methods for circadian rhythm analysis and is especially useful for populations whose circadian patterns are non-sinusoidal and irregular. On the other hand, because PML is applicable to time series data bearing a similar nature to actigraphy, the application of PML can be extended to other types of circadian rhythm studies using information such as body temperature and hormone data to study and characterize circadian rhythms effectively.

In comparison, Fisher's test for harmonic analysis tends to identify many significant periodicities unless a stringent threshold is used for statistical significance. Here we employed the Bonferroni correction to adjust for multiple testing and used the significance level 10^{-5} to select periodicities, even though we did not conduct as many statistical tests simultaneously. In sequential testing procedures like our scenario, people often use less conservative multiple testing correction methods such as the Benjamini-Hochberg procedure.[27] We chose the most stringent threshold to avoid selecting too many periodicities that are not helpful in characterizing daily activity patterns at each age.

We also compare our PML algorithm with the standard approach autocorrelation. Plots of correlation estimates against time lags are useful for identifying the correlation peak at 24 hours but not shorter periods of rhythmicity. It is because estimation of correlation can be biased due to the presence of multiple periodic rhythms, and identification of multiple periodicities by simple calculation of autocorrelation may not be accurate. Therefore, the standard approach using autocorrelation is effective in confirming the most dominant 24-hour periodicity but not as effective in identifying other periodicities, which the PML algorithm is able to achieve.

Other standard approaches such as periodograms and cosinor analysis are not used here, because there are in fact connections between PML and the two methods. It is important to point out their connections and also differences. For periodograms, the Fourier periodogram, the Enright periodogram and the Lomb-Scargle periodogram are commonly used.[14] Both our PML algorithm and the Fourier periodogram utilize Fourier analysis to identify dominant periodicities, except that the PML algorithm uses a shrinkage method in machine learning to identify dominant patterns in the population, while Fourier periodograms are focused on individuals to manually identify dominant periodicities based on individual plots. The Enright periodogram, though suitable for equidistant activity measurements in our scenario, may not be applicable here because it requires ten or more days of data.[14] In addition, the estimation method only holds when there is one periodic component, but in our case the presence of multiple periodic components may attenuate the results.[14] The Lomb-Scargle periodogram is a modification of Fourier analysis to accommodate unevenly spaced data or missing data. Because our data do not have the issue, the Lomb-Scargle periodogram is equivalent to the Fourier periodogram here. Compared with the PML algorithm, the Fourier periodogram involves more manual work to generate periodograms for each individual and visually identify dominant periodicities, while PML is more automated and also more effective in studying the population as a whole and further identifying the periodicities that are characteristic of the population. In addition, researchers often use periodograms to validate the most dominant periodicity such as 24 hours but do not specifically examine information on secondary dominant periodicities or use periodic curves to reconstruct or approximate activity patterns, even though the connection between dominant frequencies/periodicities and functional curves can be made and the periodic information can be fully utilized. Therefore, the PML algorithm makes full use of the

information from more than one dominant periodicities and links FFT results in the frequency domain with their representing cosine curves to effectively characterize activity patterns.

For cosinor analysis, recall that FFT results consist of real parts and imaginary parts that correspond to cosine curves and sine curves respectively, and thus FFT is equivalent to fitting the cosine model. We actually fitted cosine models to the activity data with one to three cosine curves at dominant periodicities identified by the PML algorithm. Even though the estimated amplitudes for the cosine curves are different from FFT results, the Pearson correlation between the cosine coefficients and the FFT signals of the same periodicity is 1, indicating equivalence. While the final results are equivalent, the procedures are different. For cosinor analysis, if prior knowledge is known, one can use simple least squares methods to fit the model.[28] However, if there is no prior knowledge on periodic information, the least squares methods cannot be used because the dominant periodicity needs to be estimated first and the cosinor model can no longer be linearized in its parameters. One has to either start from an initial guess and use iterative procedures to minimize residual sum of squares or use simulated annealing alternatively to fit the model, the process of which can be exhaustive.[29-31] In comparison, without prior knowledge on dominant periods, the PML algorithm based on shrinkage in machine learning is still easy to implement without computational burden in extracting periodic information and the results are as effective as the cosinor model to characterize daily activity patterns using cosine curves.

In summary, the proposed PML algorithm is effective in extracting periodic information, identifying dominant periodicities, and further characterizing activity patterns. In the presence of multiple periodicities, PML does not have the estimation problem that autocorrelation encounters. To identify dominant periodicities, PML uses shrinkage in machine learning methods that can avoid manual work in periodograms, which require individual plots and visual identification. PML

can also characterize activity patterns by making full use of the cosine curves represented by FFT signals and avoiding the computationally intensive process of choosing and fitting cosinor models when prior knowledge on dominant periodicities is not available.

Sleep-Activity Rhythm Characterization

Our study confirms previous study results that infants already form 24-hour sleep-wake cycles at 6 months due to entrainment by cyclical changes in the environment, whether it is due to light-dark cycles or maternal rest-activity cycles. [1, 4, 5, 32, 33] It is noteworthy that while 24-hour cycles are formed, sleep-activity patterns over the 24-hour period are not stabilized: infants often take multiple naps at different times of the day and their daily activity patterns vary across days and across individuals.

From 6 months to 12 months, our study indicates that the infant sleep-activity pattern gradually develops: some infants take only one afternoon nap while others take two naps in the morning and afternoon. Strong FFT signals at 1/3-day periodicity capture two-peak one-nap activity patterns while strong FFT signals at 1/4-day periodicity capture three-peak two-nap patterns. The results are in line with previous sleep studies that the duration of nighttime sleep gradually lengthens and sleep patterns become more and more consolidated during the first year after birth.[7, 34]

While the timing for the stabilization of infant sleep-activity patterns varies across individuals, by the time infants become 18 months old, their daily activity patterns have consolidated into a predominant nighttime pattern with one afternoon nap only, which can be obtained by combining the three dominant periodicities at 1-day, 1/2-day and 1/3-day. The consolidation of sleep-activity patterns is confirmed by increased FFT signals at 1/2-day and 1/3-day periodicities and decreased FFT signals at other periodicities compared to previous ages. The results for 24 months remain the

same as 18 months, showing no changes and confirming further that sleep-activity patterns are consolidated by 18 months and stable onwards.

In our study, the 3-hour periodicity, normally for feeding behaviors, was not detected and there might be two reasons. First, in the feeding guidelines for infants, feeding of infants aged 6-8 months are advised to be 5 to 6 times in 24 hours, less frequent than the 3-hour (8 times) schedule, and infants aged 12-24 months are advised to have three meals with family and have additional snacks for 2-3 times. [25, 26] Infants younger than 6 months may have a more frequent feeding schedule, but our activity data were collected at 6 months or later. Second, there might be desynchronization between feeding schedules and activity patterns. While 6-month infants might be fed 5-6 times per day, they do not nap or sleep 5-6 times within the same timeframe. We referred to the sleep diaries recorded by parents, and even though the diaries are less accurate due to record bias and subjectivity issues, they can be used as reference for napping information. Most 6-month infants have one to two naps in the morning and one nap in the afternoon. 12-month infants generally have one or no naps in the morning and one nap in the afternoon. Most 18-month and 24-month infants have one nap in the afternoon. Therefore, sleep-activity patterns are desynchronized with feeding schedules, as feeding behaviours might not dominate infant sleep-activity patterns at this age. For the above reasons, feeding cycles such as 3-hour periodicity were not detected in our data.

Association between Circadian Rhythms and Early Childhood Development

Using FFT signals at dominant periodicities identified by PML, we are able to find the association between the consolidation of sleep-activity rhythms and early childhood motor development. At 6 months, the association between PDMS-2 total motor scores and assessment seasons may be explained by different amounts of clothes worn by infants in different seasons. In winter, infants

are likely to wear lots of clothes, which may restrict their behaviors and result in suboptimal performances compared to infants wearing light clothes and taking the PDMS-2 assessment in summer. As a result, 6-month-old infants taking the assessment in summer and autumn got relatively higher PDMS-2 scores compared to infants in winter and spring.

Then at 12 months, after controlling for assessment seasons, stronger FFT signals at 1/2-day and 1/3-day periodicities are generally associated with higher PDMS-2 scores. 12 months is in the critical period of sleep-activity rhythm consolidation, which is captured by the growing FFT signals at 1/2-day and 1/3-day periodicities. It is noteworthy that for infants at this age, they all have strong FFT signals at 1-day periodicity, indicating that they all exhibit 1-day periodicity in their sleep-activity patterns and their 24-hour periodic activity patterns tend to be stabilized. As a result, there is not much variation in the strength of 1-day periodicity, which might not explain much of the variability in PDMS-2 scores among inidividuals. In comparison, the activity pattern over the 24-hour period is not consolidated and the activity pattern can be characterized by the 1/3-day and 1/2-day periodicities. The larger variability in the strength of 1/3-day and 1/2-day periodicities can describe the degree to which the daily sleep-activity pattern is consolidated, which is further associated with children development evaluated by PDMS-2 scores. Infants with a more consolidated activity pattern tend to have better motor development evaluations. In addition, activity rhythm consolidation is strongly associated with subcategories of locomotion and stationary, which belong to the gross motor and measure how the large muscle system is utilized to move from place to place or assume a stable posture when not moving. Therefore, we obtained new insights into early childhood development that the degree to which the sleep-activity pattern is consolidated at 12 months is associated with infant motor development and is associated with the large muscle system development in particular.

At 18 and 24 months, the PDMS-2 scores are not associated with season, FFT signals, or any other variables in the dataset we have. Most of the toddlers have stabilized daily activity patterns with strong periodic rhythmicity at this age. FFT signals as characteristics of sleep-activity rhythms are no longer associated with PDMS-2 scores, and it is likely because the critical age at which the daily activity rhythm stabilizes has passed.

In summary, the proposed PML algorithm provides a new method for circadian rhythm analysis and is particularly useful for studying populations whose patterns are not mature and regular. In addition, because the PML algorithm is applicable to time series data bearing a similar nature to actigraphy, it can be extended to other types of circadian rhythm studies using information such as body temperature data and hormone data. Therefore, the PML algorithm can be widely applied to other circadian rhythm studies to help characterize circadian rhythms based on different information. Using the proposed method, our study provides novel insights into sleep-activity rhythm development in early childhood. First, in our study, the critical time period for the consolidation of sleep-activity rhythms is between 6 and 18 months. It is because at 6 months, 24-hour sleep-wake cycles are formed but their daily activity patterns are not stabilized, and by the time toddlers become 18 months old, their sleep-activity patterns have consolidated into a fixed pattern with two activity peaks and one afternoon nap. The time period between 6 and 18 months is critical for early childhood sleep-activity rhythm development and consolidation. Second, we identified the association between the consolidation of daily rhythms and early childhood motor development, and the association is with the large muscle system development in particular. This association has not been identified in previous studies. Infants with more consolidated circadian rhythms tend to have better motor development assessments. While the mechanism is not clear, keeping a regular and stable sleep-activity pattern and maintaining a healthy circadian system are

important for healthy physical development in early childhood. Future work should investigate how circadian rhythm consolidation and motor development interrelate and contribute to early childhood development.

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Conflict of Interests

The authors have no potential conflicts of interest relevant to this article to disclose.

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Tables

Table 1. Significant periodicities at 6, 12, 18, 24 months with the corresponding proportions of variances among all Fast Fourier Transform (FFT) signals and p-values.

Age (Month)	Prop. Variance	Period (min)	Period (day)	p-value
6	0.0110	1440	1-day	6.59×10^{-8}
12	0.0120	1440	1-day	1.75×10^{-8}
12	0.0068	720	1/2-day	3.75×10^{-7}
12	0.0056	360	1/4-day	2.82×10^{-7}
12	0.0045	480	1/3-day	6.49×10^{-6}
18	0.0130	1440	1-day	1.46×10^{-9}
18	0.0085	480	1/3-day	1.87×10^{-10}
18	0.0083	720	1/2-day	5.02×10^{-15}
24	0.0130	1440	1-day	1.97×10^{-9}
24	0.0086	480	1/3-day	1.17×10^{-10}
24	0.0080	720	1/2-day	3.78×10^{-14}

Table 2. Linear regression of Peabody Developmental Motor Scales-Second Edition total motor standard scores on season and Fast Fourier Transform (FFT) signals at 6 months and 12 months, respectively.

Time	Variable	Estimate	Std. Error	t-value	p-value
6-month	(intercept)	50.10	0.56	89.52	<0.001
	spring	0.48	0.85	0.56	0.576
	summer	4.48	0.82	5.43	<0.001
	autumn	4.06	0.89	4.54	<0.001
12-month	(intercept)	45.52	1.29	35.25	<0.001
	summer	1.66	1.58	1.05	0.297
	1/2-day*	0.19	0.09	2.10	0.039
	1/3-day*	0.31	0.09	3.55	<0.001
	summer:1/3-day*	-0.48	0.16	-3.00	0.004

* FFT signals were multiplied by 10,000 in regression models so that the estimated effect sizes are for every 10,000-unit increase in FFT signals.

Table 3. Linear regression of Peabody Developmental Motor Scales-Second Edition standard scores on season and Fast Fourier Transform (FFT) signals at 12 months: stationary and locomotion subtests, gross motor and fine motor as the outcome respectively.

Category	Variable	Estimate	Std. Error	t-value	p-value
Stationary	(Intercept)	9.23	0.19	47.9	<0.001
	1/3-day	0.04	0.02	2.17	0.033[a]
Locomotion	(Intercept)	7.16	0.43	16.48	<0.001
	summer	0.71	0.75	0.94	0.348
	1/3-day	0.19	0.04	4.61	<0.001[a]
	summer: 1/3-day	-0.13	0.07	-1.93	0.057[b]
Gross Motor	(Intercept)	26.41	0.63	42.03	<0.001
	summer	0.57	1.09	0.52	0.602
	1/3-day	0.24	0.06	3.97	<0.001[a]
	summer: 1/3-day	-0.17	0.10	-1.73	0.087[b]
Fine Motor	(Intercept)	21.08	0.5	42.15	<0.001
	summer	0.34	0.86	0.39	0.697
	1/3-day	0.11	0.05	2.36	0.021[a]
	summer: 1/3-day	-0.15	0.08	-1.89	0.062[b]

* FFT signals were multiplied by 10,000 in regression models so that the estimated effect sizes are for every 10,000-unit increase in FFT signals.

[a] Statistical significance level at α=0.05.

[b] Statistical significance level at α=0.10.

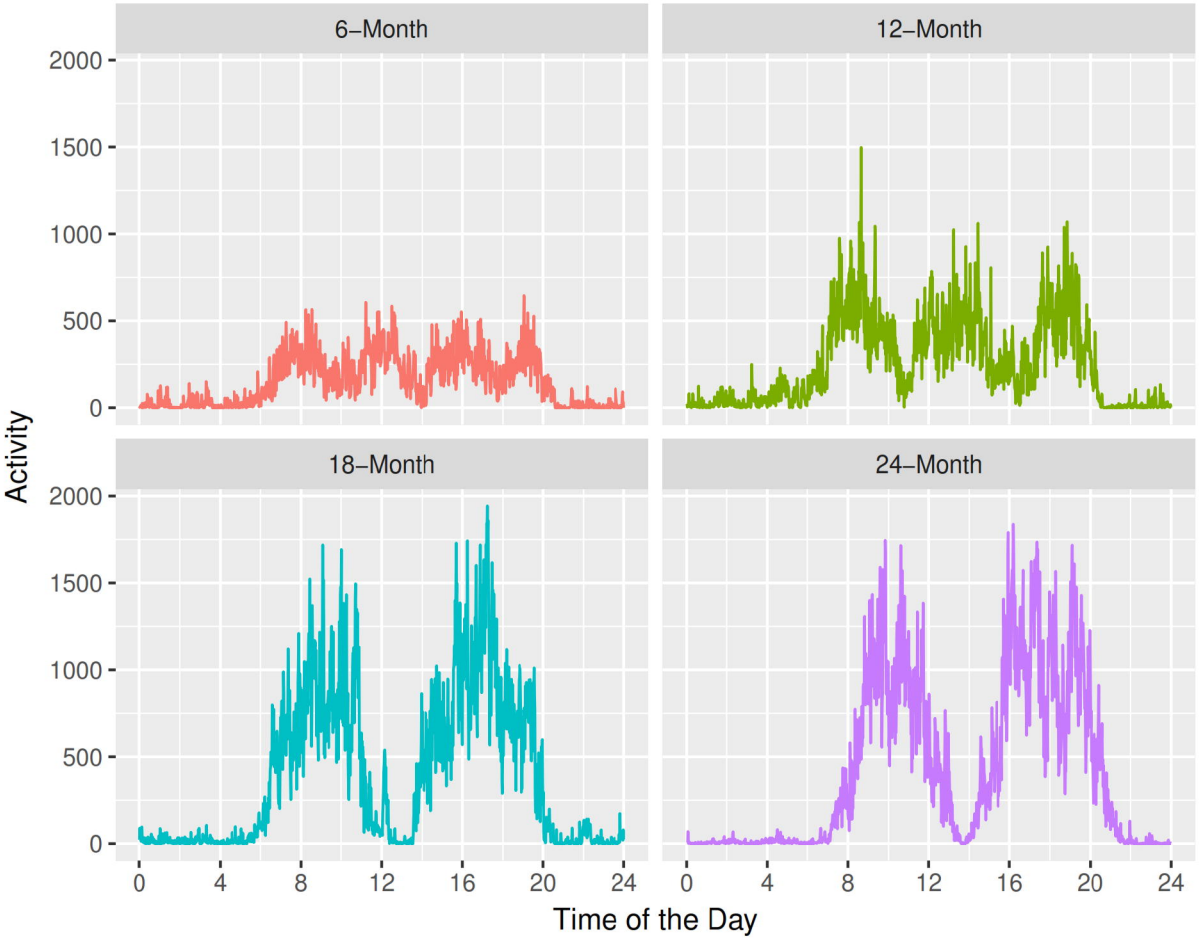
Figures

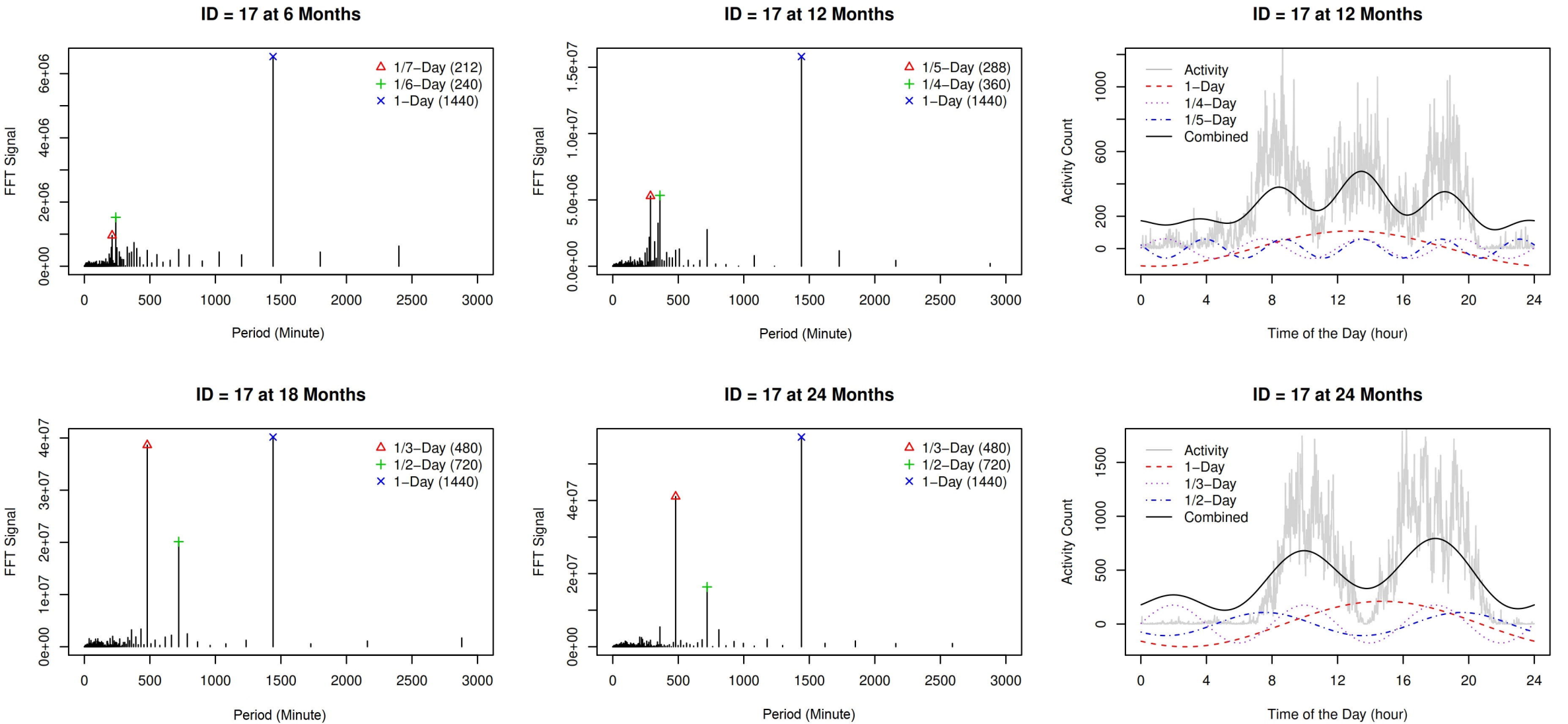
Figure 1. The activity plots for ID 17 at 6, 12, 18, and 24 months respectively, with activity counts averaged across seven days at each time point.

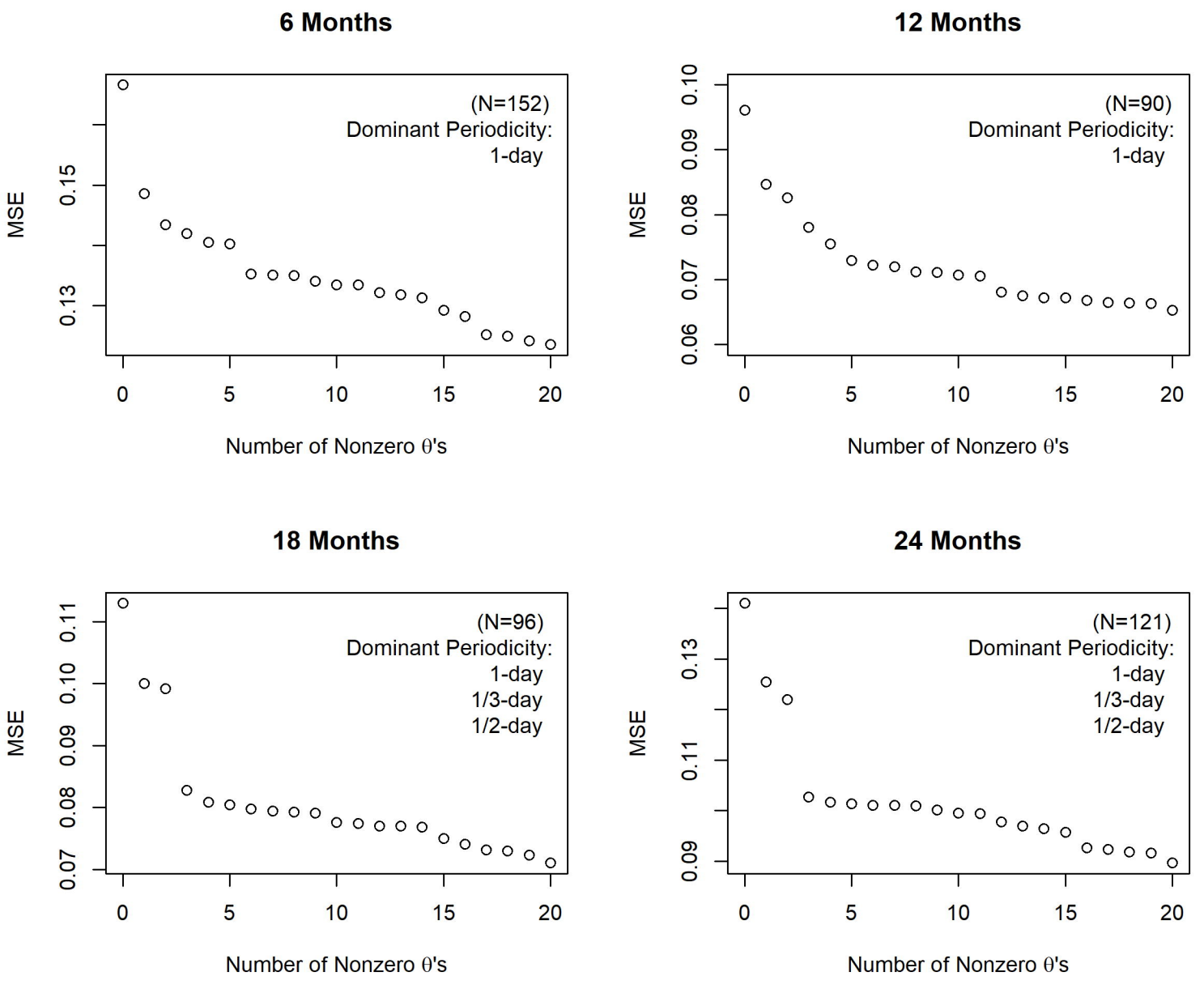
Figure 2. Left panel: Fast Fourier Transform (FFT) results for ID 17 at 6, 12, 18, and 24 months, respectively. Right panel: top three periodicities and the combined plotted on 1-day observation for ID 17 at 12 months and 24 months, respectively.

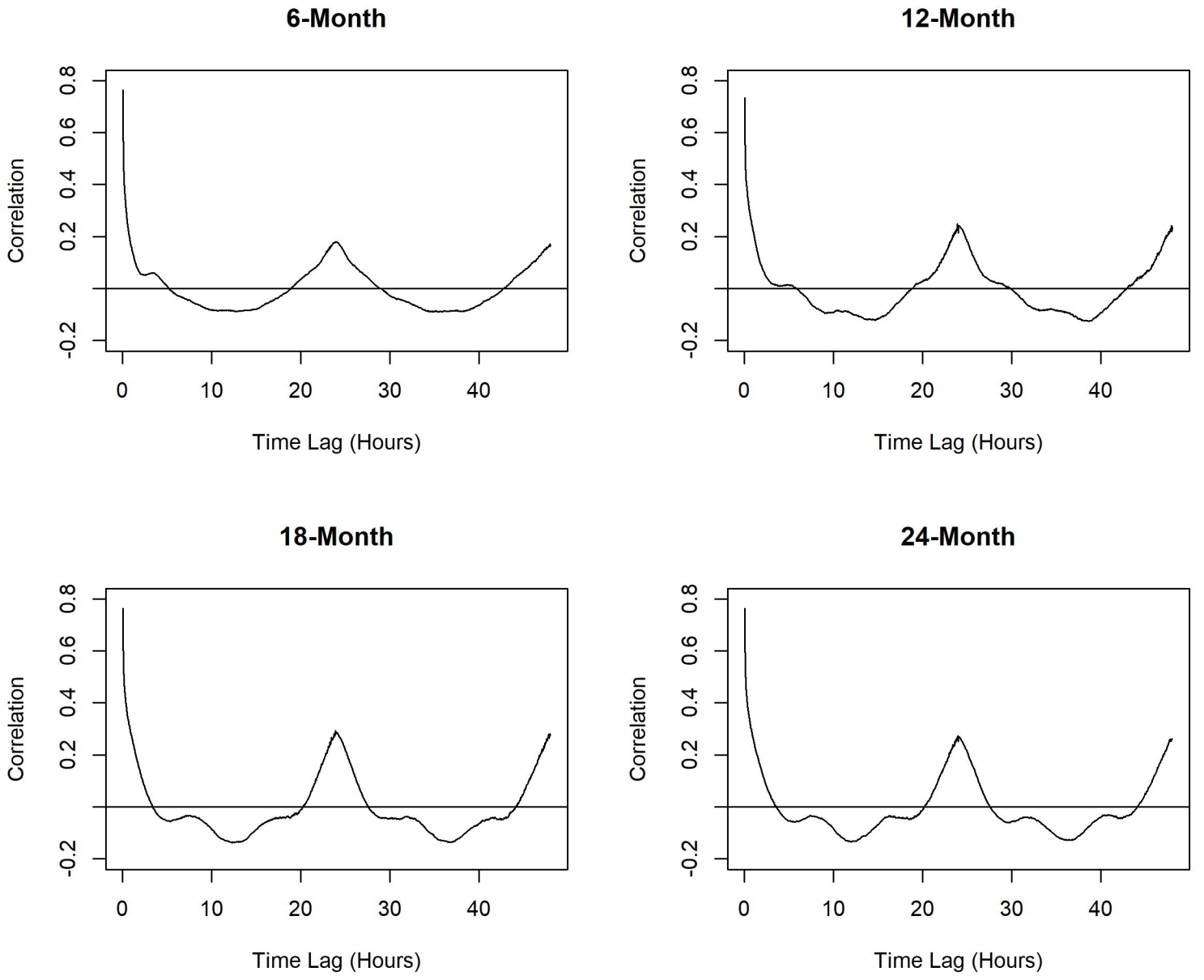
Figure 3. Mean squared error (MSE) against the number of nonzero θ's as the penalty term λ decreases, at 6, 12, 18, and 24 months, respectively.

Figure 4. Estimated autocorrelation against time lags at 6, 12, 18, and 24 months respectively.


6–Month
12–Month
18–Month
24–Month
Activity
2000
1500
1000
500
0
0
4
8
12
16
20
24
Time of the Day


ID = 17 at 6 Months
FFT Signal
Period (Minute)
1/7−Day (212)
1/6−Day (240)
1−Day (1440)
ID = 17 at 12 Months
FFT Signal
Period (Minute)
1/5−Day (288)
1/4−Day (360)
1−Day (1440)
ID = 17 at 12 Months
Activity Count
Time of the Day (hour)
Activity
1−Day
1/4−Day
1/5−Day
Combined
ID = 17 at 18 Months
FFT Signal
Period (Minute)
1/3−Day (480)
1/2−Day (720)
1−Day (1440)
ID = 17 at 24 Months
FFT Signal
Period (Minute)
1/3−Day (480)
1/2−Day (720)
1−Day (1440)
ID = 17 at 24 Months
Activity Count
Time of the Day (hour)
Activity
1−Day
1/3−Day
1/2−Day
Combined


6 Months
(N=152)
Dominant Periodicity:
1-day
MSE
0.13
0.15
0
5
10
15
20
Number of Nonzero θ's
12 Months
(N=90)
Dominant Periodicity:
1-day
MSE
0.06
0.07
0.08
0.09
0.10
0
5
10
15
20
Number of Nonzero θ's
18 Months
(N=96)
Dominant Periodicity:
1-day
1/3-day
1/2-day
MSE
0.07
0.08
0.09
0.10
0.11
0
5
10
15
20
Number of Nonzero θ's
24 Months
(N=121)
Dominant Periodicity:
1-day
1/3-day
1/2-day
MSE
0.09
0.11
0.13
0
5
10
15
20
Number of Nonzero θ's


6-Month
12-Month
18-Month
24-Month
Correlation
Time Lag (Hours)
-0.2
0.2
0.4
0.6
0.8
0
10
20
30
40