Between-laboratory and Demographic Effects on Heart Rate and Its Variability During Sleep

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Abstract. This work statistically analyzed the between-laboratory and demographic effects on cardiac activity during sleep in a multi-laboratory sleep monitoring study. A multilevel analysis was employed to evaluate these effects on two cardiac parameters expressing heart rate and heart rate variability. Results show that the two parameters vary between sleep stages and from subject to subject while there are no differences found between laboratories. In addition, these two parameters exhibit differently for subjects varied in their demographics.

Keywords: Cardiac activity, sleep stages, between-laboratory effect, demographics, multilevel analysis

1 Introduction

Nighttime sleep for adults consists of wake, rapid-eye-movement (REM) sleep, and four non-REM (NREM) sleep stages S1-S4 according to the rules recommended by Rechtschaffen and Kales (R&K rules) [1]. The gold standard for sleep analysis is polysomnography (PSG), with which sleep stages are manually scored by sleep technicians through visually inspecting the multi-channel physiological signals in PSG [1].

Cardiac activity, or more specifically, heart rate and its variability, is known to be related to sleep stages due to the regulation of autonomic nervous system, which has been intensively investigated for sleep assessment [2, 3]. The cardiac data in PSG is usually collected in a sleep laboratory. In a multi-laboratory study, the effects caused by using different PSG configurations on the measurements can be calibrated. However, it is not clear whether the cardiac activity varies between laboratories possibly caused by, e.g., the difference of sleeping environment, stress, or measurement errors. Additionally, cardiac activity also corresponds to subject demographics such as age, sex, and/or body mass index (BMI), which has been shown in previous studies (e.g., [4]). Therefore, we aimed

at statistically analyzing the between-laboratory and the demographic effects on heart rate and its variability during sleep.

A multilevel analysis [5] was employed to perform statistical analysis of the above-mentioned effects. In comparison with the traditional methods including analysis of variance (ANOVA) and multivariate ANOVA, multilevel analysis has some advantages. For example, it is a more generalized regression analysis considering hierarchical variables with effects on multiple levels simultaneously so that the effects are easier to be interpreted and it can handle missing data instead of simply excluding them. These advantages fit well to our data with several hierarchical levels including laboratory, subject, and measurement.

2 Methods

2.1 Subjects and Data

Single-night PSG recordings of 165 healthy subjects (88 females, age 51.8 ± 19.4 years, BMI 24.6 ± 3.5 kg/m^2) from the SIESTA database [6] were included. They were collected from seven laboratories and the (adult) subjects had ages across the human lifespan (from 20 to 95 years). Based on the PSG recordings, sleep stages were scored on consecutive 30-s epochs by two unique sleep technicians according to the R&K rules and the consensus of annotations applied between the two scorers in case of disagreement. Here we considered wake, REM sleep, light sleep (merged S1 and S2 sleep), and deep sleep (merged S3 and S4 sleep) and we analyzed a total amount of 134,017 epochs.

The cardiac data from the PSG recordings were used for analysis, where heartbeats were detected from ECG using a slope-based QRS localization algorithm [7]. We considered two cardiac parameters: mean heart rate (HR) and standard deviation of heartbeat intervals (SDNN), which were computed within each 30-s epoch. Since these two parameters were found to be skewed distributed, they were transformed by nature logarithm (ln).

2.2 Multilevel Analysis

Multilevel analysis can be used on hierarchical data with fixed and random effects, which can be expressed as a generalized linear regression model for a response variable and its corresponding predictors [5]. Considering simple two-level data with only one predicting variable, the multilevel model is given by

$$\begin{aligned} &y_{ij} = \beta_0 + u_{0j} + (\beta_1 + u_{1j})x_{ij} + \varepsilon_{0ij}, \\ &\text{with } \begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \Omega_0 \\ \Omega_1 \end{bmatrix} \right) \text{ and } \varepsilon_{0ij} \sim N(0, \Omega_\varepsilon), \end{aligned} \tag{1}$$

where x_{ij} is the i-th observation from group j, y_{ij} the associated response, β_0 the fixed intercept), β_1 the fixed slope, u_{0j} the random intercept, u_{1j} the random slope, and ε_{0ij} the residual term. The model consists of fixed effects (intercept and slope) and random effects (intercept and slope). The random effects and the residual variance should follow a normal distribution with zero mean.

2.3 Between-laboratory and Demographic Effects

Here we construct multilevel models with three levels to analyze the between-laboratory and demographic effects on the cardiac parameters (level one: epoch-based measurement, level two: subject, and level three: laboratory). For a given parameter (HR or SDNN), the model is

$$\begin{aligned} y_{ijk} = {} & \beta_0 + v_{0k} + u_{0jk} + \beta_w wake_{ijk} + \beta_r REM_{ijk} + \beta_l light_{ijk} + \beta_d deep_{ijk} \\ & + \beta_{sex} sex_{jk} + \beta_{age} age_{jk} + \beta_{bmi} BMI_{jk} + \varepsilon_{0ijk} \end{aligned} \tag{2}$$

$$\text{with } \begin{bmatrix} v_{0k} \\ u_{0jk} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \Omega_{v_{0k}} \\ \Omega_{u_{0jk}} \end{bmatrix} \right) \text{ and } \varepsilon_{0ijk} \sim N(0, \Omega_\varepsilon),$$

where y_{ijk} is the parameter value of the i-th epoch of the night from subject j monitored in laboratory k, β_0 is the fixed intercept, v_{0k} is the level-three coefficient with random effect $\Omega_{v_{0k}}$ that indicates the between-laboratory variation, u_{0jk} is the level-two coefficient with random effect $\Omega_{u_{0jk}}$ expressing the physiological difference from subject to subject, $wake_{ijk}$, REM_{ijk}, $light_{ijk}$, and $deep_{ijk}$ are a group of dummy variables specifying the sleep stage of the epoch with their respective fixed effect (β_w, β_r, β_l, or β_d), sex (0 = male, 1 = female), age, and BMI are demographic variables with fixed effects β_{sex}, β_{age}, and β_{bmi}, respectively, and ε_{0ijk} is the error term with a variance of Ω_ε indicating the variation within subjects. All random effects and the error variance are assumed to be normally distributed, which was confirmed using a Q-Q plot method.

We implemented the multilevel models using the software package MLwiN [8], developed by the Centre for Multilevel Modeling, University of Bristol, UK. In the package, the iterated generalized least square (IGLS) algorithm was used to estimate the models' coefficients and the associated variances. The model goodness-of-fit to the data can be measured by the model deviances (i.e., -2·log-likelihood) obtained during multilevel modeling. We applied a Wald test to assess the statistical significance of a specific effect. In other words, it served to test if the effect has significant deviation from zero. The Wald statistic Z is the square of the estimated coefficient θ divided by its standard error (SE) such that $Z = [\theta/\mathrm{SE}(\theta)]^2$, tested using a Chi-squared test with one degree of freedom.

3 Results and Discussion

Table 1 presents the results of the multilevel analysis for HR and SDNN. The association between cardiac activity and sleep stages was confirmed as shown in the table. We also see that for both parameters, no significant effects were found in the laboratory level; while the variances in the subject level presented significantly. Regarding the demographic effects between subjects, women had a higher heart rate ($\beta_{sex} = 0.047$ for HR, $p < 0.05$) and a smaller heart rate variability ($\beta_{sex} = -0.281$ for SDNN, $p < 0.001$) than men. In addition, SDNN decreased along with the increase of age ($\beta_{age} = -0.010$, $p < 0.001$) and BMI ($\beta_{bmi} = -0.024$, $p < 0.05$). These findings indicate that, instead of the differences between laboratories, the variation of HR and SDNN during sleep can be

Table 1. Estimated coefficients and variances of multilevel models for HR and SDNN

	ln HR [bpm]	ln SDNN [ms]		ln HR [bpm]	ln SDNN [ms]
Fixed	Estimates (SE)		β_{age}	0.0004 (0.0006)†	-0.010 (0.002)*
β_0	4.045 (0.080)*	4.912 (0.275)*	β_{bmi}	0.004 (0.003)†	-0.024 (0.012)**
β_w	Baseline	Baseline	Random	Estimates (SE)	
β_r	-0.043 (0.001)*	-0.029 (0.005)*	$\Omega_{v_{0k}}$	0.0002 (0.0005)†	0.000 (0.000)†
β_l	-0.068 (0.001)*	-0.006 (0.003)**	$\Omega_{u_{0jk}}$	0.018 (0.002)*	0.223 (0.025)*
β_d	-0.054 (0.001)*	-0.237 (0.005)*	Ω_{ε}	0.004 (1.7e-5)*	0.263 (0.001)*
β_{sex}	0.047 (0.022)**	-0.281 (0.075)*	Deviance	-348724.9	202199.9

Note: For each estimates, statistical significance was examined using a Wald test ($^{*}p < 0.001$, $^{**}p < 0.05$, †not significant).

mainly explained by sleep stages and by individual differences with respect to demographics and cardiac physiology. Note that in this study using two unique sleep technicians to score all the data might also influence the results in a favorable manner, which needs to be further investigated.

4 Conclusion

Using a multilevel analysis, we revealed that there was no between-laboratory effect on heart rate and its variability during sleep. Instead, the subject-level variances (independent of sleep stages) indicate the existence of physiological differences between subjects. In regard to demographics of the studied samples, women had a higher heart rate and a smaller heart rate variability than men, where the latter decreased along with the increase of age and body mass index.

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