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## Time delay between cardiac and brain activity during sleep transitions

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Human sleep consists of wake, rapid-eye-movement (REM) sleep, and non-REM (NREM) sleep that includes light and deep sleep stages. This work investigated the time delay between changes of cardiac and brain activity for sleep transitions. Here, the brain activity was quantified by electroencephalographic (EEG) mean frequency and the cardiac parameters included heart rate, standard deviation of heartbeat intervals, and their low- and high-frequency spectral powers. Using a cross-correlation analysis, we found that the cardiac variations during wake-sleep and NREM sleep transitions preceded the EEG changes by 1–3 min but this was not the case for REM sleep transitions. These important findings can be further used to predict the onset and ending of some sleep stages in an early manner. © 2015 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4917221>]

In the past decades, a phenomenon has been recognized in many domains that two coupled sources or systems exhibit an unsynchronized interaction with a time difference or delay in between.<sup>1–6</sup> For instance, neural oscillators have enhanced coupling in delayed-time.<sup>2</sup> In particular, this may occur during transitions between two physical or biological states such as chaotic state changes,<sup>3</sup> gene switches,<sup>4</sup> neutron emission,<sup>5</sup> and cardiorespiratory phase synchronization transitions.<sup>6</sup> Understanding these phenomena can help, e.g., explore the coherence of neurons and information transmission of the brain in neurology<sup>2</sup> and improve “perception-action” planning with stimulus events from external world in cognitive science.<sup>7</sup>

In this letter, we apply the time delay analysis in the area of human sleep. Neurophysiological mechanisms of sleep are exceptionally important for humans to maintain, for instance, health, internal homeostasis, memory, and cognitive and behavioral performance.<sup>8,9</sup> Numerous studies have reported significant association between heart rate (and heart rate variability, HRV) and electroencephalographic (EEG) activity during sleep, where they both vary across sleep states/stages.<sup>10–12</sup> Previous studies have demonstrated the presence of unsynchronized changes of HRV and EEG activity in time course over the entire night.<sup>13,14</sup> However, the variations of brain activity and autonomous cardiac dynamics should not be independent of sleep (state/stage) transitions, for which their coupling might change. We therefore investigated the time delay in sleep transition profiles between cardiac and EEG activity using a cross-correlation analysis, which was not studied before.

It is known that human sleep consists of wake state, rapid-eye-movement (REM) sleep state, and non-REM (NREM) sleep state including four stages 1, 2, 3, and 4

according to the rules recommended by Rechtschaffen and Kales (R&K).<sup>15</sup> With the more recent guidelines of the American Academy of Sleep Medicine,<sup>16</sup> stages 3 and 4 are suggested to be merged to single slow wave sleep or “deep” sleep since no essential difference was found between them. Besides, stages 1 and 2 usually correspond to “light” sleep. According to one of these manuals, sleep states/stages are scored by sleep clinicians on continuous 30-s epochs by visually inspecting polysomnographic (PSG) recordings including multi-channel EEG, electrooculography (EOG), and electromyography (EMG).

A total of 330 overnight PSG recordings in the SIESTA database<sup>17</sup> from 165 normal subjects (88 females) were considered in our analysis, where each subject spent two consecutive nights for sleep monitoring.<sup>18</sup> The subjects had an average age of  $51.8 \pm 19.4$  y and the average total recording length was  $7.8 \pm 0.5$  h per night. They fulfilled several criteria such as no reported symptoms of neurological, mental, medical, or cardiovascular disorders, no history of drug or alcohol abuse, no psychoactive medication, no shift work, and retirement to bed between 22:00 and 24:00 depending on their habitual bedtime. Sleep states/stages were scored by two independent raters based on the R&K rules. In case of disagreement, the consensus annotations were obtained. The inter-rater reliability (measured by Cohen’s Kappa coefficient of agreement<sup>19</sup> ranging from 0 to 1) in separating different sleep stages is compared in Fig. 1. It shows that the Kappa in distinguishing between light and deep sleep was statistically significantly lower than that for separating other sleep stages. This is due to the gradual changes of physiological behaviors within NREM sleep.

The EEG activity was quantified by a parameter  $f_{\text{EEG}}$ , called EEG mean frequency.<sup>13</sup> To calculate it, the EEG signals were first band-pass filtered between 0.3 and 35 Hz and then the power spectral density was computed for each

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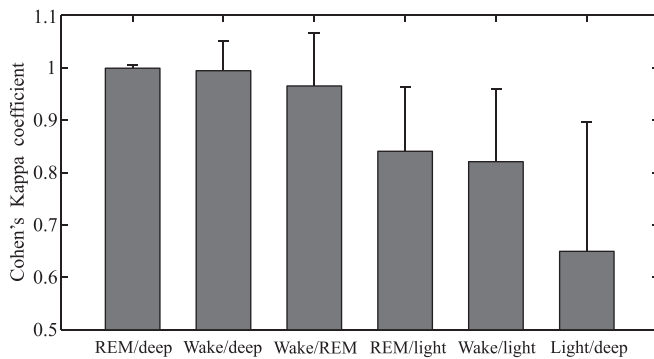


FIG. 1. Inter-rater agreement as evaluated by Cohen's Kappa [mean and SD over recordings] between different sleep stages. Statistical significance of difference between each two Kappa values was examined with a t-test, where the Kappa had no significant difference between REM sleep/deep sleep and wake/deep sleep and between REM sleep/light sleep and wake/light sleep ( $p < 0.05$ ) but it was significantly different between the others ( $p < 0.001$ ).

non-overlapping 2-s interval with a discrete Fourier transform (DFT). Afterwards, the associated peak frequencies between 0.5 and 30 Hz were detected accordingly and then for each 30-s epoch, they were averaged over a window of 9 epochs (4.5 min) centered on that epoch, yielding the epoch-based estimates of  $f_{EEG}$ . The cardiac parameters, derived from electrocardiography (ECG) signals over a 9-epoch window centered on each 30-s epoch, included mean heart rate (HR), standard deviation of heartbeat intervals (SDNN), and the logarithmic spectral powers of heartbeat intervals in low-frequency (LF, 0.01–0.15 Hz) and high-frequency (HF, 0.15–0.4 Hz) bands. They have been proven to relate to certain properties of autonomic nervous system.<sup>20,21</sup> For instance, HR, SDNN, and LF are associated with sympathetic activity and the HF power is a marker of parasympathetic or vagal activity activated by respiratory-stimulated stretch receptors.<sup>21–23</sup> Many studies have shown that autonomic nervous activity is effective in identifying sleep states or stages when PSG is absent.<sup>24–26</sup> Here, all the parameters were normalized to zero mean and unit variance (Z-score) for each recording, leading to a normalized unit “nu.” Note that the use of a window aimed at including sufficient heartbeats to capture cardiac rhythms and to help reduce signal noise so that the autonomic nervous activity can be reliably expressed where a window size of about 5 min was recommended.<sup>23</sup>

This could also help reduce signal noise. For analyzing the time delay during sleep transitions, we chose 30 s the minimum epoch length because (1) it is the standard resolution for PSG-based manual scoring of sleep stages<sup>15</sup> and (2) using a smaller length the parameters could be influenced by the subtle changes caused by the physiological response during arousals,<sup>27</sup> which would likely lead to spurious cross-correlation analysis results. Fig. 2 illustrates an example of overnight sleep profile and the EEG and the cardiac parameter values from a healthy subject. It can be seen that these parameters seem correlated with sleep states/stages to some extent.

To capture the delayed changes of cardiac and EEG activity, we constrained our analysis on the periods with 15 epochs (7.5 min) before and after each transition moment where only one transition occurred in the middle of each period. The amount of these periods was 1077 out of totally

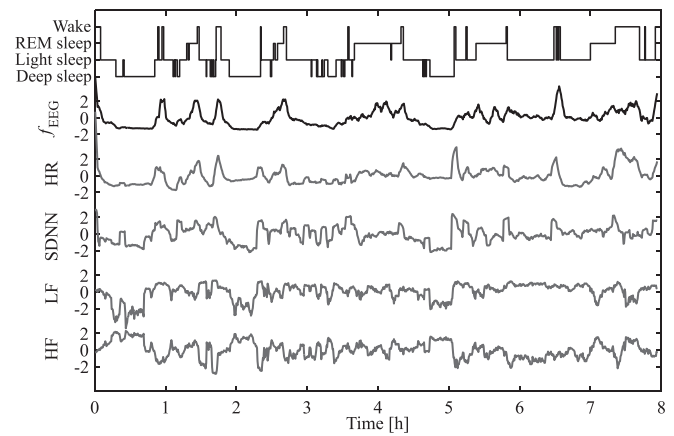


FIG. 2. An example of epoch-based sleep states/stages over night and the normalized (Z-score) EEG mean frequency  $f_{EEG}$  and cardiac parameters HR, SDNN, LF, and HF (in nu).

28 359 transitions from all 330 recordings.<sup>28</sup> The first and the last 5 epochs of these periods were excluded, yielding 10-min segments used for analyzing time delays. This served to avoid the time-delayed effects of the previous and the next transitions when analyzing the parameter values for the time delay of current sleep transition and, meanwhile, to include enough data points for computing cross-correlation coefficients. By these means, we only considered major types of sleep transitions in three “hierarchical” levels, as shown in Fig. 3. They are the transitions: (1) between wake and sleep including  $W \rightarrow LS$  (from wake to light sleep),  $LS \rightarrow W$  (from light sleep to wake), and  $RS \rightarrow W$  (from REM sleep to wake); (2) between REM and NREM sleep including  $RS \rightarrow LS$  (from REM to light sleep) and  $LS \rightarrow RS$  (from light to REM sleep); and (3) within NREM sleep including  $LS \rightarrow DS$  (from light to deep sleep) and  $DS \rightarrow LS$  (from deep to light sleep). These seven types of transitions are of predominance among all sleep transitions,<sup>29,30</sup> which can also be observed in our data (see Fig. 3). The transitions between REM and deep sleep and from deep sleep to wake were not included. For each parameter, we calculated the mean values over all the 10-min segments for each type of transition and then they were Z-score normalized. Fig. 4 illustrates the mean parameter values 5 min (or 10 epochs) before and after sleep transitions.

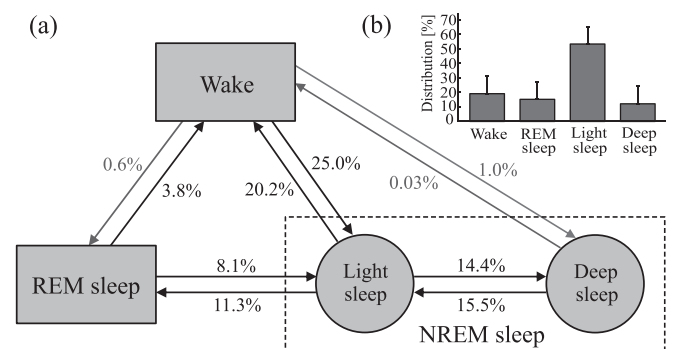


FIG. 3. (a) Mean percentages of sleep transitions over recordings. The average number of total transitions per recording is 85.9. The transitions are indicated with arrows, where the REM–deep sleep transitions are not shown because they account for less than 0.01% of total transitions. (b) Sleep stage distribution (mean and SD over recordings).

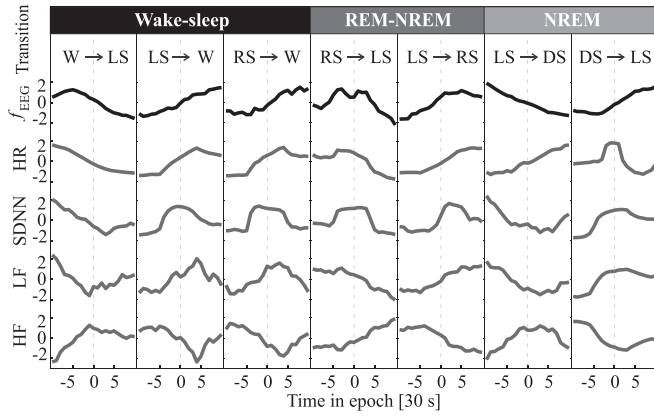


FIG. 4. Mean values of the normalized parameter  $f_{\text{EEG}}$ , HR, SDNN, LF, and HF (in nu) with 10 epochs (5 min) before and after different sleep transitions.

The cross-correlation between EEG mean frequency  $f_{\text{EEG}}$  and each cardiac parameter  $\alpha_c$  (HR, SDNN, LF, or HF) for a given time segment with  $m$  epochs is expressed by a cross-correlation function  $G$

$$G_{f_{\text{EEG}}, \alpha_c}(n) \equiv (f_{\text{EEG}} \star \alpha_c)(n) = \frac{1}{m} \sum_{i=1}^{m-n} f_{\text{EEG}, i} \cdot \alpha_{c, i+n}, \quad (1)$$

where  $n$  is the number of time shifts (a.k.a. time lag) of the convolution between  $f_{\text{EEG}}$  and  $\alpha_c$ . Therefore, the delayed time  $\Delta\tau$  can be obtained by searching for the lag leading to maximum absolute correlation coefficient, such that

$$\Delta\tau = \arg \max_n |G_{f_{\text{EEG}}, \alpha_c}(n)|. \quad (2)$$

The time delay  $\Delta\tau$  can be positive or negative. A positive  $\Delta\tau$  value indicates that  $f_{\text{EEG}}$  starts changing earlier than the cardiac parameter  $\alpha_c$ , and conversely, a negative value reflects that the variations of  $\alpha_c$  are later than  $f_{\text{EEG}}$  with  $\Delta\tau$  epochs ( $\Delta\tau/2$  min) on average.

As shown in Table I, the cardiac parameters started changing approximately 1.5 min ahead of the EEG mean frequency for the entire-night recordings, confirming the findings reported by Otzenberger *et al.*<sup>13</sup> This indicates that the changes of autonomous activity generally precede the EEG changes. It was also revealed that on average HR, SDNN, and LF were positively correlated with EEG mean frequency, while HF was negatively correlated with it ( $p < 0.05$ ). In addition, the table provides the time delay analysis results for different types of sleep transitions, where the time lag  $\Delta\tau$  (in 30-s epoch) and the associated maximum correlation coefficients  $r$  are given. For SDNN, LF, and HF, we found that the time lag was of  $-3$  to  $-1$  min for the transitions between wake and sleep and of  $-2$  to  $-1$  min for NREM sleep transitions. This indicates that the changes of HRV anticipated the variations of EEG mean frequency by 1–3 min for these types of transitions. In general, the relatively constant time delay between cardiac and EEG parameters indicates the existence of time differences between autonomic and cortical changes during sleep transitions. The constant earlier appearance of autonomic variations suggests that cortical changes are secondary to changes elsewhere in

TABLE I. Results of time delay  $\Delta\tau$  (in 30-s epoch) between EEG mean frequency  $f_{\text{EEG}}$  and four cardiac parameters HR, SDNN, LF, and HF for different sleep transitions. Correlation coefficients  $r$  were computed for lags from  $-20$  to  $+20$  epochs. For full-night recordings, the average time delays and correlation coefficients are presented which were significant ( $p < 0.05$ ) for the majority of the recordings (82.7% for HR, 85.2% for SDNN, 76.1% for LF, and 78.4% for HF). For sleep transitions, the maximum correlations are presented and they were found to be significant ( $p < 0.0001$ ). The positive delays mean that EEG changes are prior to cardiac changes and the negative delays indicate the changes in cardiac activity preceding those in EEG activity.

Sleep transition	HR		SDNN		LF		HF	
	$\Delta\tau$	$r$	$\Delta\tau$	$r$	$\Delta\tau$	$r$	$\Delta\tau$	$r$
Full-night recording								
All, $N = 330$	-2.4	0.22	-2.6	0.24	-2.6	0.19	-3.3	-0.19
Wake-sleep transition								
W $\rightarrow$ LS, $N = 159$	-1	0.90	-3	0.86	-5	0.71	-4	-0.77
LS $\rightarrow$ W, $N = 84$	-1	0.89	-5	0.62	-2	0.74	-2	-0.73
RS $\rightarrow$ W, $N = 29$	-2	0.86	-6	0.70	-3	0.79	-3	-0.86
REM-NREM transition								
RS $\rightarrow$ LS, $N = 180$	0	0.84	0	0.90	0	0.71	0	-0.71
LS $\rightarrow$ RS, $N = 284$	1	0.89	0	0.84	1	0.92	2	-0.90
NREM transition								
LS $\rightarrow$ DS, $N = 196$	0	-0.96	-2	0.70	-2	0.75	-3	-0.64
DS $\rightarrow$ LS, $N = 145$	1	-0.60	-4	0.78	-4	0.81	-4	-0.83

the brain (e.g., brain stem) or central nervous system. These time differences are sleep state/stage dependent and seem not occurring for REM sleep (i.e., REM-NREM transitions). This also suggests that the physiology of these changes during REM sleep is different from that during wake and NREM sleep. In fact, REM sleep has different physiological mechanisms compared with NREM sleep, where REM transitions are “switch-like” transitions,<sup>31</sup> while the physiological variations within NREM sleep are gradual.<sup>32</sup> The lack of time delay during REM transitions might also be caused by the fact that the R&K rules force human raters to merge REM epochs of 30 s into one REM sleep period if they occur within 3 min.<sup>15</sup> For W  $\rightarrow$  LS transitions, upon a closer look, we found that most of them were in the beginning of the night, indicating the presence of time delay conveyed between cardiac and brain activity during sleep onset. The time delay from sleep (REM or light sleep) to wake could be due to the gradual steps of awakening.<sup>33,34</sup> Additionally, as shown in the table, the changes of HR seem always later than the HRV changes. We therefore speculate that, to a certain degree, parasympathetic changes (reflected by HF changes) might present slightly earlier than the variations of sympathetic activity (corresponding to HR changes) during wake-sleep and NREM transitions.

As stated, when computing the parameters, we applied averaging or filtering over a 9-epoch (4.5-min) window centered on each epoch in order to obtain reliable parameter values. Fig. 5 illustrates the time delay and the associated absolute correlation coefficient versus the averaging window size. The figure shows that our choice was appropriate where the correlations generally increased and the time delays  $\Delta\tau$  stabilized along with the increase in window size. In fact, when performing cross-correlation analysis between two signals, using a symmetric linear-phase filtering at the same

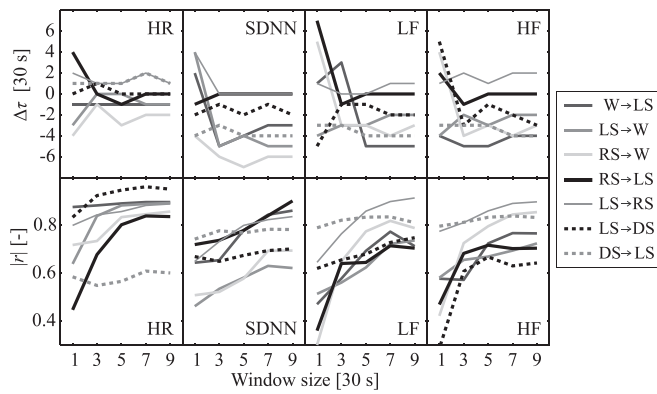


FIG. 5. Time delay  $\Delta\tau$  between cardiac and EEG activity and the associated (maximum) absolute correlation coefficient  $|r|$  versus averaging window size (1–9 epochs and step size 2 epochs) for computing the epoch-based parameters.

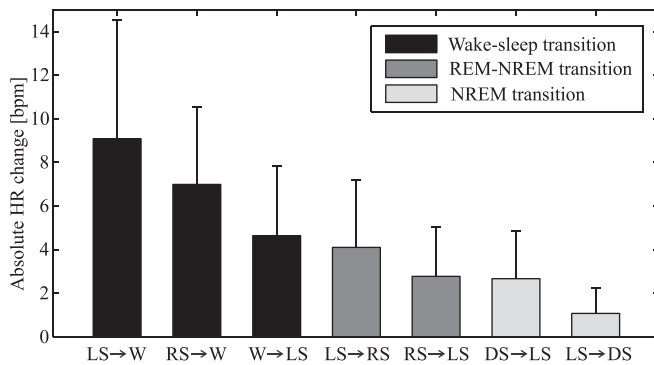


FIG. 6. Absolute (maximum) changes of HR during sleep transitions (mean and SD), computed based on the 10-min segments.

window size would not cause signal phase distortion.<sup>35</sup> Thus, the averaging here should not affect the lag sought when searching for the time delays.

Fig. 6 shows the absolute changes of HR (in beat per minute, bpm) during different sleep state/stage transitions. It is noted that large HR changes (4.6–9.1 bpm) occurred during the wake-sleep transitions, while the NREM transitions had the smallest changes in HR (1.1–2.7 bpm). This supports the “hierarchical” nature of the various transitions and confirms the validity of the results.

In summary, we investigated the time delay between cardiac and brain activity for different sleep transitions using a cross-correlation analysis. The presented results indicate that the autonomic nervous system changes generally precede the EEG changes by 1–3 min during sleep transitions except for REM-NREM transitions. In practice, the important findings here can be used in future research to predict sleep state/stage changes based on autonomic nervous activity.

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