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SCIENTIFIC INVESTIGATIONS

The abrupt shift to slower frequencies after arousal from sleep in healthy young adults

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Study Objectives: Postarousal hypersynchrony (PAH) is an atypical arousal pattern in children's electroencephalography. PAH is an abrupt shift to slower frequencies in arousal-related responses, appearing as slow-wave clusters. In contrast, the prevalence of PAH in healthy young adults is still unknown. Here, we examined the prevalence and characteristics of PAH in healthy young participants.

Methods: Thirty healthy young participants underwent 1 night of polysomnography (13 females, 22.8 ± 2.0 years [mean ± standard deviation]). We examined the prevalence of PAH as a function of sleep stage, sleep cycle, and time course (the first or the second half). The correlation between PAH and sleep variables was examined. The percent of total sleep time in the N3 stage (%N3) was compared for each sleep cycle and time course.

Results: Twenty-eight out of 30 participants exhibited PAH (4.6 ± 4.8 times per night). PAH increased significantly during the first sleep cycle and the first half-sleep period. It was observed only in nonrapid eye movement and not in rapid eye movement sleep. The number of PAHs correlated with the number of arousals and arousal indices. The %N3 increased in the first half-sleep and the first sleep cycle.

Conclusions: PAH was relatively common in healthy young participants. Since PAH occurred in a state with a high prevalence of %N3, the first sleep cycle, or the first half-sleep, we suggest that PAH may be affected by the sleep homeostasis process. Since PAH occurred only in non-rapid eye movement sleep and correlated with arousal increment, it may have the function of suppressing non-rapid eye movement sleep's cortical arousal.

Keywords: arousal, electroencephalogram, sleep, delta activity

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Healthy children often exhibit postarousal hypersynchrony, which is an abrupt shift to slower electroencephalographic frequencies after arousal. However, the prevalence and characteristics of postarousal hypersynchrony in healthy young participants remain unknown.

Study Impact: We have clarified that postarousal hypersynchrony had a relatively high prevalence (93.3%) in healthy young participants. The number of postarousal hypersynchronies increased during N3, the first half-sleep, and the first sleep cycle, when corrected for the number of arousals. We suggest that postarousal hypersynchrony may be affected by the sleep homeostasis process, which may suppress the cortical arousal of non-rapid eye movement sleep.

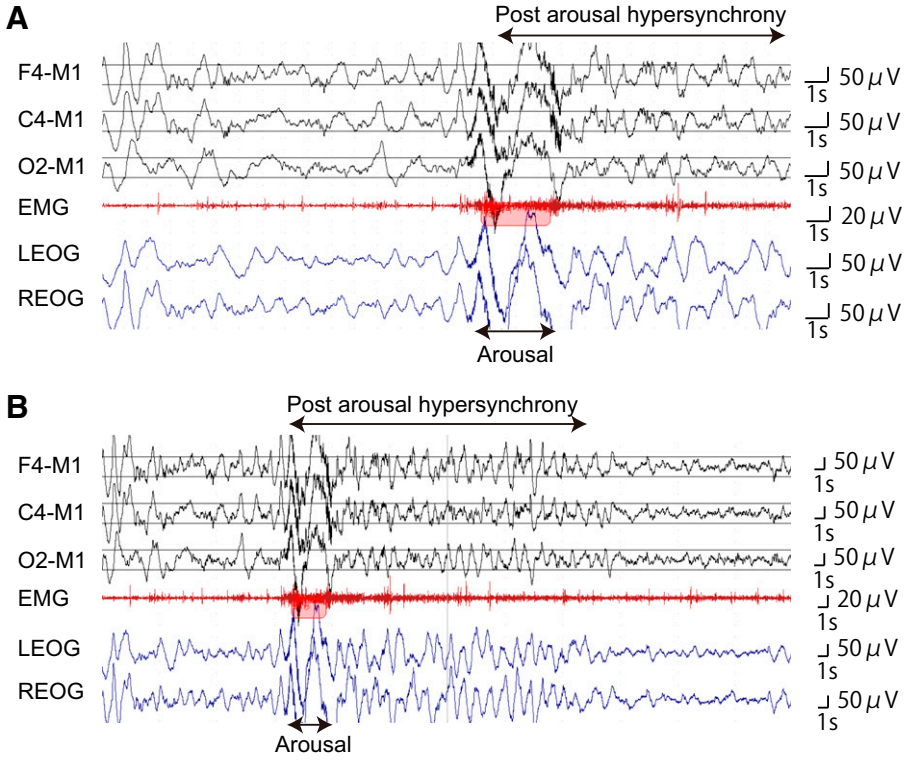
INTRODUCTION

Postarousal hypersynchrony (PAH) is an atypical arousal pattern in the electroencephalogram (EEG) during sleep. It was first introduced in a healthy pediatric EEG activity by Kellaway and Fox.[1] The PAH shown in healthy children is a high-voltage sinusoidal rhythm after the arousal reaction.[1] This activity is seen predominantly in the frontal region in an EEG.[1] The prevalence of this phenomenon appears most frequently between the 12th and 18th month after birth and tends to decline in the degree of expression after the age of 2 years, but it still exists in healthy children for up to 4–5 years.[1] Although it appears in children,[1,2] the prevalence of spontaneous PAH in healthy young adult participants remains unclear. Furthermore, responses to external auditory stimulation in healthy young adults are induced concomitant with the K-complex or bursts of delta waves.[3–5] Since we observed several PAHs in the polysomnography (PSG) of healthy young adults in our routine PSG scoring (**Figure 1**), we anticipated that the prevalence of PAH may be relatively high in healthy young adults; nevertheless, it is called an "atypical" arousal pattern in EEG.

Since delta bursts in non-rapid eye movement (NREM) parasomnias increase in N3[6–9] and the first half-sleep[6–8,10] and are affected by sleep pressures,[6] we thought that the PAH may be similarly affected by sleep pressure in healthy participants. Therefore, we examined changes in PAH numbers as sleep stages, sleep cycles, and time (the first or the second half-sleep).

This study aimed to evaluate PAH in healthy young participants, examining the prevalence and characteristics of the atypical arousal responses. First, we examined the prevalence of the atypical arousal responses in healthy young participants. Second, we investigated the hypothesis that PAH activity in healthy young participants would arise prominently in the first half-sleep and sleep stage N3, where sleep pressure would be high.[11–15]

Figure 1—An example of postarousal hypersynchrony.



(A) A polysomnogram at the 30-second epoch. **(B)** The polysomnogram extended the 60-second epoch. EMG = electromyogram, LEOG = left electrooculogram, REOG = right electrooculogram.

METHODS

Thirty healthy participants (13 females) aged 22.8 ± 2.0 [18–27] years (mean ± standard deviation [range]) were included in this study. This was not a 3-part study, but the subjects were recruited in three studies. The first study was an intervention test for procedural memory. The second study was an observational study of the menstrual cycle.[16] The 2 studies recruited participants through posters on the University of Tsukuba website. The third study was a portable sleep EEG device validation study based on simultaneous measurements using PSG and the device, and participants were recruited via e-mail using the mailing list of the University of Tsukuba. Participants who had a history of sleep disorders were excluded. No participants had a prior history of NREM parasomnias. Written informed consent was obtained from each participant. The Institutional Review Board approved the data collection and usage (Approved ID# H29-177).

One PSG was used from each participant for this study. The PSGs were recorded in the three studies. In the first study, all 10 PSGs from the main test recording night were the same experimental trials. The second study included 2 participants' PSG in the first night as the adaptation night.[16] Furthermore, the third project protocol was a single-night sleep study for 18 participants. In the first study, the PSG results from the first night were excluded. Two participants who were included in the second study underwent PSG on the first night. In the third study, we did not confirm whether this was the first PSG that had been undergone in 18 participants; thus, up to 20 of 30 participants could have undergone a first-night PSG recording.

The PSG was performed using standard electrode montages: electroencephalography (EEG, inductions were F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, and O2-M1), electrooculography, and chin electromyography. PSGs were recorded using Polysmith software and PSG-1100 (Nihon Kohden, Tokyo, Japan). The sampling frequency was set at 250 Hz for EEG, electrooculography, and electromyography. For the EEG and electrooculography, the low-frequency and high-frequency filters were set at 0.3 and 35 Hz, respectively. The electromyography was filtered from 10 to 100 Hz. Based on the American Academy of Sleep Medicine (AASM) scoring rules, sleep recordings were divided into 5 discrete stages (stage W, N1, N2, N3, and R), including arousals.[17] Total recording time, total sleep time (TST), sleep efficiency, percent of total sleep time for each stage (%N1, %N2, %N3, and %R), sleep latency, slow-wave sleep latency, stage R latency, wake after sleep onset, and arousal index were obtained from these records according to the criteria established by the AASM.[17]

Delta bursts after arousal were defined as PAH by referring to the AASM scoring guideline[17] and previous PAH literature.[1,2,18,19] The PAH was detected over 6 different derivations of EEG throughout the participants' whole recording and

immediately after arousal. The PAH event was scored if it contained at least 5 seconds of continuous high-voltage (≥ 75 μV) delta waves (0.5–4 Hz) in the frontal lead (F4-M1) in all sleep stages (**Figure 1**). Simultaneously, other EEG electrodes were used as references for the delta waves' synchronicity. The PAH endpoint was determined when the delta burst amplitude was decreased to < 75 μV. An experienced registered polysomnographic technologist (the second author) detected the number of PAHs. We evaluated the mean, minimum, and maximum PAH durations for all participants.

The number of PAH events per night for each participant and the number of participants who showed PAH was evaluated. The number of PAHs was computed for each sleep stage, the first or the second half (divided into 2 parts based on total recording time), and each sleep cycle. Sleep cycles were defined according to Feinberg and Floyd.[20] The frequency of PAH or arousal was calculated by dividing the number by sleep duration (the duration of the sleep stage, the first or the second half, and sleep cycles). The PAH ratio relative to arousals was also calculated for each sleep stage, the first or the second half, and each sleep cycle.

The EEG spectrograms of PAH were analyzed to evaluate the PAH spatial distribution on the scalp. The EEG spectrogram was computed by BrainVision Analyzer software version 2.2.0 (Brain Products, Gilching, Germany) for the EEG-derived data from F4-M1, C4-M1, and O2-M1, with a bandpass filter set at 0.3–35 Hz for the EEG signals. The EEG power spectra were computed for 4.096-second (ie, 1,024 points) windows without overlap in each EEG channel after removing a direct current component and applying the 10% 2-sided tapered cosine window. The fast Fourier transform was evaluated to estimate the spectral power density (μV^2/Hz). The delta EEG frequency band was from frequencies between 0 and 3.99 Hz based on the AASM criteria.[17] The epochs containing high-frequency or low-frequency artifacts, such as body movement, clenched teeth, or sweat drift in any channel, were visually inspected and removed from all of the EEG signals at F4-M1, C4-M1, and O2-M1 for the subsequent averaging. Finally, the logarithmically transformed power spectra of artifact-free epochs were averaged for each participant.

The slow-wave activity (SWA) is an index of the homeostatic process S that reflects sleep needs.[11,12] Since SWA or length of N3 decreases in sleep, the earlier part of sleep is affected by higher sleep pressure.[13–15] We aimed to determine the decrease in %N3 over time by comparing the first half and the second half of %N3 sleep and among sleep cycles. Correlation coefficients of age, the Pittsburgh Sleep Quality Index,[21] the Japanese version of the Morningness-Eveningness Questionnaire,[22] and sleep indices against the numbers of PAH and arousals were examined using Pearson's correlation coefficient or Spearman's rank correlation. Twenty-six out of 30 participants answered the Pittsburgh Sleep Quality Index (4.7 ± 2.0) and Morningness-Eveningness Questionnaire (49.2 ± 6.8) and were found to have regular sleep habits.

All statistical analyses were performed using Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL). The normality test was carried out using the Shapiro-Wilk test. For nonnormally distributed parameters, the Friedman test, Wilcoxon signed-rank test, or Spearman's rank correlation coefficient analysis was used. For normally distributed parameters, a one-way repeated-measures analysis of variance (degrees of freedom were corrected with the Greenhouse-Geisser correction), paired *t* test, and Pearson's correlation coefficient were used. The Wilcoxon signed-rank tests with Bonferroni's correction were preferred for multiple comparisons of the Friedman tests. Paired *t* tests with Bonferroni's corrections were used for post hoc tests for a one-way repeated-measures analysis of variance. The significance level was set at $P < .05$.

RESULTS

No one showed symptoms of NREM parasomnias, such as a typical attack of sleepwalking. We indicate sleep parameters in **Table S1** in the supplemental material.

To study the change in sleep pressure over time, we compared %N3 between the first half and the second half-sleep and each sleep cycle. The %N3 significantly increased in the first half-sleep than in the second half-sleep (**Figure S1A** in the supplemental material, $Z = 4.74$, $P < .05$). Since 24 participants reached sleep cycle 4, we compared sleep cycles in these participants. The %N3 in each sleep cycle varied significantly ($\chi^2 = 34.05$, $P < .05$). There were significant differences among each sleep cycle (**Figure S1B**, cycle 1 vs cycle 2: $Z = 3.29$; cycle 1 vs cycle 3: $Z = 4.29$; cycle 1 vs cycle 4: $Z = 4.20$; cycle 2 vs cycle 4: $Z = 3.44$; all *P* values < .05). The results showed that %N3 in cycle 1 was the largest among the sleep stages (**Figure S1B**).

Twenty-eight out of 30 participants (93.3%) exhibited PAH. The average and median numbers of occurrences were 4.6 ± 4.8 and 3.0 times, respectively. The mean PAH duration was 12.7 ± 6.3 seconds, and the minimum and maximum values were 5 and 40 seconds, respectively. Although only 1 participant showed a PAH during stage W (stage N1 and N2 were < 15 seconds in the epoch), we included the PAH in the following analyses because of the agreement of the PAH criteria used in the study. The PAH appeared exclusively in NREM sleep and most frequently during N2, followed by N3 and N1 (**Table 1**). The number of PAHs corrected by sleep duration varied significantly among sleep stages (**Figure 2A**, $\chi^2 = 49.10$, $P < .05$). Pairwise tests showed that these frequencies of PAH events in each NREM sleep stage were significantly higher compared with the frequency of PAH in stage W (stage N1 vs W: $Z = 3.78$; N2 vs W: $Z = 3.46$; N3 vs W: $Z = 3.52$; all *P* values < .05) and R (stage N1 vs R: $Z = 3.82$; N2 vs R: $Z = 4.11$; N3 vs R: $Z = 3.52$; all *P* values < .05) (**Figure 2A**). There were no significant differences in the frequencies of PAH among NREM sleep stages (**Figure 2A**). The ratio of PAH events relative to arousal number also showed significant differences among the stages (**Figure 3A**, $\chi^2 = 50.09$, $P < .05$). Since 3 out of 30 did not show arousal in N3, we removed the participants to analyze the PAH events' ratio by arousal in each sleep stage. The ratio of PAH in NREM sleep stages was significantly higher than that in stage W (stage N1 vs W: $Z = 3.39$; N2 vs W: $Z = 3.82$; N3 vs W: $Z = 3.53$; all *P* values < .05), and in REM sleep (stage N1 vs R: $Z = 3.62$; N2 vs R: $Z = 3.92$; N3 vs R: $Z = 3.53$; all *P* values < .05) (**Figure 3A**). The ratio showed a significant difference between stages N3 and N1 (N1 vs N3: $Z = -3.33$, $P < .05$) (**Figure 3A**). The PAH was

Table 1—Characteristics and prevalence of postarousal hypersynchrony.

	Sum	Minimum	Maximum	Mean ± SD	Median
Sleep stage					
All	138	0	18	4.6 ± 4.8	3
N1	31	0	3	1.0 ± 1.0	1
N2	71	0	14	2.4 ± 3.4	1
N3	35	0	9	1.2 ± 1.9	1
R	0	0	0	0.0 ± 0.0	0
W	1	0	1	0.0 ± 0.2	0
Half divided TRT					
First half	116	0	15	3.9 ± 4.3	2
Second half	22	0	3	0.7 ± 0.8	1
Sleep cycle†					
Cycle 1	56	0	9	2.3 ± 2.8	1
Cycle 2	51	0	6	2.1 ± 2.0	2
Cycle 3	18	0	5	0.8 ± 1.1	0.5
Cycle 4	5	0	2	0.2 ± 0.5	0

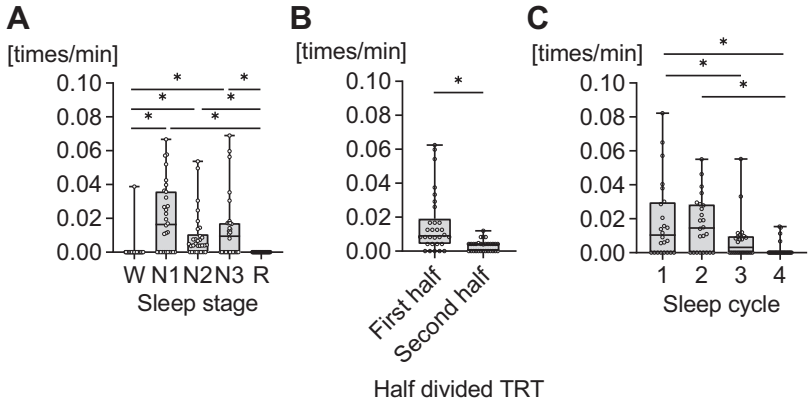
†Data from 24 out of 30 participants who reached sleep cycle 4 were analyzed. SD = standard deviation, TRT = total recording time.

significantly intensified in the first half-sleep than in the second half-sleep when corrected for both sleep duration and arousal number (**Figure 2B**, $Z = 4.15$; **Figure 3B**, $Z = 3.95$; all P values < .05). Since 24 out of 30 participants reached sleep cycle 4, we used them to analyze the sleep cycle. The number of PAHs modified by sleep duration or arousal number varied significantly (**Figure 2C**, $\chi^2 = 22.53$; **Figure 3C**, $\chi^2 = 18.67$; all P values < .05). The number of PAHs corrected for sleep duration and arousal number showed significant differences between the first and fourth sleep cycle (**Figure 2C**, $Z = 3.33$; **Figure 3C**, $Z = 2.92$; all $P < .05$) as well as between the second and fourth sleep cycle (**Figure 2C**, $Z = 3.53$; **Figure 3C**, $Z = 3.24$; all $P < .05$). Only the number of PAHs corrected for sleep duration showed a significant difference between the first and third cycle (**Figure 2C**, $Z = 2.78$, $P < .05$).

Table S2 shows the characteristics and prevalence of arousal. The number of arousals increased in N1 and decreased in N3. This number in each sleep stage, modified by sleep stage duration, varied significantly (**Figure 4A**, F (1.73, 50.10) = 106.77, $P <$ .05). There were significant differences among each arousal density except for N1 vs W and N2 vs R (stage N1 vs N2: $t = 20.24$; N1 vs N3: $t = 20.83$; N1 vs R: $t = 15.82$; N2 vs W: $t = -8.02$; N2 vs N3: $t = 9.21$; N3 vs R: $t = -5.88$; N3 vs W: $t = -9.46$; R vs W: $t = -7.25$; all $P < .05$). There was a significant difference in the ratio of arousal between the first and second half of total recording time (**Figure 4B**, $t = 2.69$, $P < .05$). The arousal ratio showed no effects on the sleep cycle (**Figure 4C**, F (3, 69) = 1.91, $P = .14$).

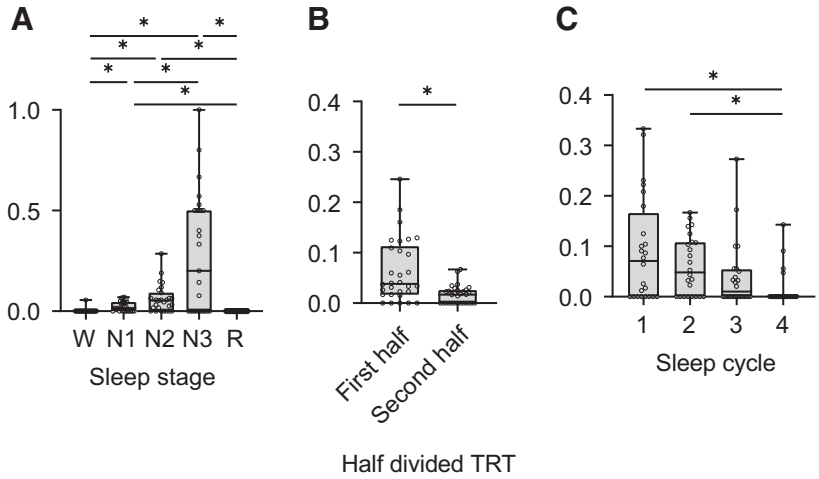
The number of PAHs and arousal during the entire sleep period showed no correlation with age, the Pittsburgh Sleep Quality

Figure 2—Frequencies of PAH were modified by each stage's duration, the first or second half-sleep, and sleep cycle.



(A) Numbers of PAH divided by duration in each sleep stage. **(B)** PAH activities divided by the first or the second half of total recording time. **(C)** PAH numbers divided by the duration of each sleep cycle. Boxes show interquartile ranges from 25%–75%. Whiskers indicate the range between maximum and minimum. Data points are plotted with circular dots. *P < .05. PAH = postaraousal hypersynchrony, TRT = total recording time.

Figure 3—PAH ratios were divided by the arousal numbers in each sleep stage, the first or second half-sleep, and sleep cycle.



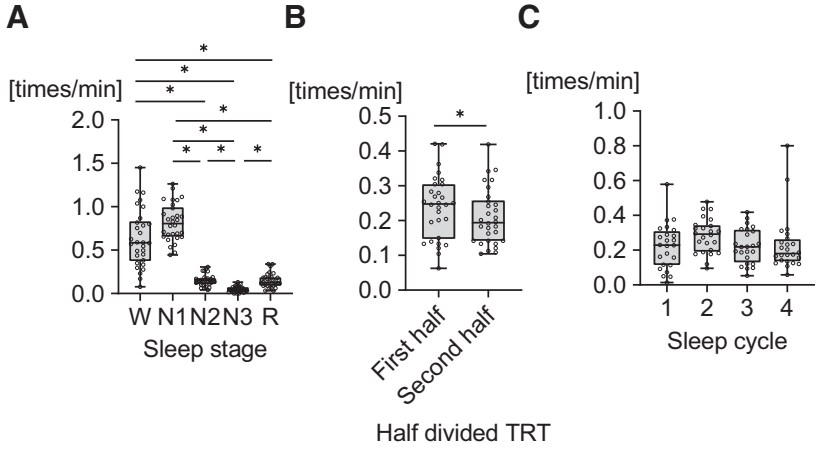
(A) PAH numbers, corrected by dividing the number of arousals in the sleep stage. The 3 participants who showed no arousals in stage N3 were removed from the statistics. **(B)** PAH activities divided by the number of arousals in the first and second half of total recording time. (C) PAH numbers modified by the arousal number of each sleep cycle. Boxes show interquartile ranges from 25%–75%. Whiskers indicate the range between maximum and minimum. Data points are plotted with circular dots. *P < .05. PAH = postarousal hypersynchrony, TRT = total recording time.

Index score, or the Morningness-Eveningness Questionnaire score (**Table S3**). The correlations of sleep indices with the number of PAHs or arousals are shown in **Table 2**. PAH significantly correlated with total arousal number, especially in NREM sleep (stage N1, N2, and N3) and arousal index, whereas arousal was not correlated with PAH in stage R (**Table 2**). Although the total number of arousals significantly correlated with the arousal number of W, N1, N2, and N3, there was no correlation between the total number of arousals and the number of arousals in R (**Table 2**). We analyzed 21 out of 28 participants who showed PAH for the delta band EEG frequency because no epoch remained after artifact rejection in seven participants. An analysis of variance of the delta band EEG on PAH revealed a significant main effect of electrode: F (1.28, 25.63) = 70.20, P < .05. Post hoc analysis revealed that the F4-M1 electrode exhibited the highest delta band EEG power, whereas the O2-M1 electrode had the lowest (ΔF4-C4 = 0.23, t = 8.35; ΔF4-O2 = 0.50, t = 9.08; and ΔC4-O2 = 0.27, t = 6.85; all P values < .05) (**Figure 5**).

DISCUSSION

Twenty-eight out of 30 participants exhibited PAH (4.6 ± 4.8 times per night). The PAH was observed in NREM and not in

Figure 4—Number of arousals modified by each sleep stage's duration, the first or second half-sleep, and sleep cycle.



(A) The number of arousals divided by length in the sleep stage. **(B)** Arousal activities divided by the first or the second half of the total recording time. **(C)** Arousal numbers modified by dividing the duration of each sleep cycle. Boxes show interquartile ranges from 25%–75%. Whiskers indicate the range between maximum and minimum. Data points are plotted with circular dots. *P < .05. TRT = total recording time.

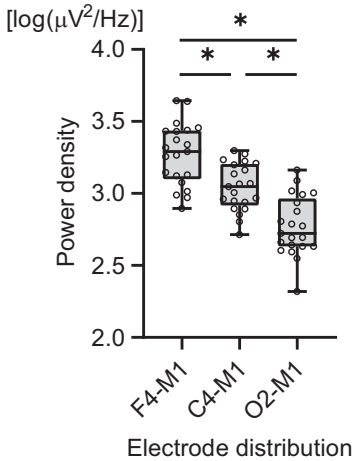
Table 2—Correlation analyses in sleep indices against PAH or arousal number.

Sleep Index	PAH		Arousal Number	
	r_s	*P*	r_s (*r*)	*P*
TST (min)	.29	.12	−.19	.33
%N1	.21	.28	.71	< .05
%N2	−.10	.58	−.44†	< .05
%N3	.27	.15	.20	.30
%R	−.30	.11	−.15†	.42
SE (%)	.06	.74	−.26	.17
SL (min)	.35	.06	.07	.70
SWSL (min)	.23	.22	−.09	.63
Stage R latency (min)	.07	.72	.16	.40
WASO (min)	−.21	.28	.30	.10
Arousal number (times)	.44	< .05	NA	NA
W (times)	−.11	.56	.51†	<.05
N1 (times)	.36	< .05	.90†	<.05
N2 (times)	.38	< .05	.75†	<.05
N3 (times)	.56	< .05	.49	<.05
R (times)	−.01	.96	.23	.23
Arl (times/h)	.41	< .05	.98†	<.05

†Pearson correlation analysis, since these parameters were normally distributed. We analyzed the correlation between arousal number and %N2, %R, arousal in W, arousal in N1, arousal in N2, and arousal index for Pearson's correlation. Arl = arousal index, NA = not applicable, PAH = postarousal hypersynchrony, SE = sleep efficiency, SL = sleep latency, SWSL = slow-wave sleep latency, TST = total sleep time, WASO = wake after sleep onset.

REM sleep. The number of PAHs increased by N2, by N1 when corrected for sleep length, and by N3 when corrected for arousal. The PAH rose significantly during the first sleep cycle and the first half-sleep. The power of PAH increased in the frontal region.

Figure 5—Box and whisker plot showing the distribution of delta band EEG power during the postarousal hypersynchrony.



The highest delta EEG frequency power can be observed in F4-M1. Boxes show the interquartile ranges from 25%–75% of the delta band EEG power, and whiskers indicate the range between maximum and minimum. Data points are plotted with circular dots. *P < .05. EEG = electroencephalogram.

Arousal increased at N1 and decreased at N2 and N3 after correction for sleep length. The PAH was significantly correlated with arousal numbers, arousal index, and arousal numbers in N1, N2, and N3, indicating that the more the arousal, the more the PAH. Arousal decreased in the second half-sleep more than in the first half-sleep, but there was no change in the sleep cycle.

Our study showed that the PAH activity was relatively common in healthy young participants. We found that the PAH activity increased during the first half-sleep period and the first sleep cycle, which contained a high amount of SWS, which is also evident from our results (**Figure S1**). The SWS is an index of the homeostatic process S that reflects sleep needs.[11,12] Since it decreases during the course of sleep, the earlier part of sleep is considered to be affected by the higher sleep pressure.[13–15] Therefore, considering the dominant timing of PAH, its occurrence may be affected by sleep pressure. We could examine this hypothesis in the future by investigating whether the PAH after sleep deprivation would increase.

PAH may be affected by the sleep homeostasis process, but it could also be a marker of process S. A putative marker of process S is thought to be SWA.[12,13] Therefore, further studies are needed to clarify the significance of PAH by examining the similarities and differences between SWA and PAH.

Unlike PAH, the number of arousals was dominant in N1, but decreased in N3. Younes et al[23] clarified that the arousal threshold was the lowest in stage N1 and the highest in sleep stage N3, which was consistent with our arousal results. Therefore, our results may reflect the change in arousal threshold variety in sleep depth. The

number of arousals was relatively higher in the first half-sleep than in the second half-sleep, whereas there were no changes among the sleep cycles. Previous studies showed that the arousal number was stable in each sleep cycle,[24,25] which was consistent with our results. Because of this, we believe that sleep pressure may affect arousal less than PAH.

Sleep scoring of PAH during light NREM sleep (N1 and N2) has no consensus rule. There has been no discussion on the effect of PAH on sleep staging during N1 and N2.[1,2,18,19] When PAH occurs, there are slow-wave bursts at high voltage that would be scored as stage N3 following the AASM manual.[17] Butkov[26] scored the epoch, which contained PAH as stage N3. On the contrary, Grigg-Damberger[27] showed a postarousal delta activity from N3 in a 13-year-old and proposed that this delta shift in pediatric EEG may be scored as stage N1 because sleep depth may not be deepened immediately after arousal. Whether PAH should be contained during arousal or SWA is still debatable.[26,27] Earlier studies support the notion that PAH should not be considered as SWS.[18,19,27] According to our research, a relatively high prevalence of PAH occurs in stages N1 and N2. If we define PAH activities as the SWA, there would be inconsistent sleep stages that would occur frequently. Since the sleep depth may not be deepened immediately after arousal,[27] we propose that the PAH should not be scored as delta waves, and the epoch should be scored with the same arousal rule of AASM.[17] If PAH occurs during stage N1, N2, and N3, it should be scored as normal arousal, excluding PAH as a slow wave. This rule could solve the scoring inconsistency in PAH by its inclusion in the AASM scoring guidelines, which would improve intrarater and interrater reliability of PSG scoring.

In this study, no participant showed PAH during stage R. Recently, Honjoh et al[28] clarified that optogenetic stimulation of ventromedial thalamic nucleus cells rapidly aroused mice from NREM, but not from REM sleep. There may be a difference in the arousal pathway in the thalamus between NREM and REM sleep.[28] The REM sleep is characterized by desynchronization on the EEG.[29] The neurophysiological changes in REM sleep include cerebral activation in the neocortex, specific sensory relay nuclei, and the limbic system.[30] This activation requires participation in brain stem structures, including a restricted pontine area.[31] On the contrary, the NREM sleep's physiological correlates include decreased function of the brain stem ascending arousal pathway and synchronization of unspecific thalamocortical connections.[31] Furthermore, our data suggested that the number of arousals during REM sleep was not correlated with total arousal numbers, unlike NREM. This may result in different characteristics between NREM and REM arousals. Since our study showed that the PAH occurred only during NREM sleep, it can be concluded that PAH may be regulated by the NREM-specific arousal system.

There were similarities between PAH in children[1,2,19,32] and our data in healthy young adults. First, previous studies showed that PAH was frontal dominant.[1,2,19,32] We examined the distribution of the PAH using fast Fourier transform and clarified that PAH was dominant in the frontal region. The other similarity between previous studies[19,32] and our study was that PAH was observed to occur in the sleep stages N1, N2, and N3, but not in REM sleep. Therefore, we think that the PAH in young adults arises in a similar mechanism as that in children.

The EEG in NREM parasomnias also shows similar delta waves as the PAH, called hypersynchronous delta activity (HSD).[6,9] The PAH in healthy young participants in this study and HSD in NREM parasomnias showed similar characteristics.[6,8–10,33,34] First, the PAH in young adults of our study and HSD in young adult NREM parasomnia[6] occurred in the frontal region. Our result in healthy young participants, which demonstrated frontal dominance of the delta band EEG power in the PAH, is consistent with HSD's previous results in young adult NREM parasomnia.[6] Second, PAH and HSD occur in both children and adults. The HSD in NREM parasomnia occurred not only in children,[7] but also in adults.[6,8–10,33,34] Our research also extended the notion that PAH occurs in healthy young adults, which adds to the similarities between PAH and HSD. Third, our study showed that PAH increased in SWS and the first half-sleep and disappeared during REM. In a previous study, HSD also appeared only in the first half of NREM sleep (stage N2 and N3) and increased in stage N3.[6] This similarity suggests that HSD and PAH are affected by sleep pressure. These similarities imply that the occurrence of PAH may share partial properties of HSD.

Meanwhile, there were at least two differences between HSD and PAH. First, HSD appearance is not always accompanied by arousal.[6,9] On the contrary, PAH is an arousal-related response. A hypothesis called "local sleep," a phenomenon in which parts of the brain could be asleep while other parts are awake,[35] has been used to explain HSD in NREM parasomnias.[36] A previous study using intracerebral stereo-EEG demonstrated that local wake-like brain activity, "local arousals,"[37] occurs during confusional arousal events in NREM parasomnia.[36,38] The coexistence of wake-like and sleep-like EEG patterns in different brain cortex areas are assumed to prevent smooth transition to awakening in NREM parasomnia.[36,38–44] Although PAH occurs with arousal, it is unknown whether PAH is accompanied by local arousal. It is also not known what initiates the coexistence of local sleep and local arousal during HSD. Future studies are needed to answer these questions: whether local arousal also appears in PAH and what triggers local sleep and arousal during HSD. Second, there are no reports of HSD in NREM parasomnias in stage N1, but our study showed PAH in stage N1. However, the current research could not clarify why there are no reports of HSD in NREM parasomnias in stage N1, whereas our study showed that PAH was frequent in stage N1. Future studies are needed for a direct comparison to determine the reasons for these differences between HSD and PAH.

From the EEG microstructure viewpoint, we discuss the relationship between the cyclic alternating pattern and PAH. The cyclic alternating pattern is a periodic EEG activity during NREM sleep.[24] It is characterized by sequences of transient electrocortical events (A-phase) which are distinct from the background EEG activity (B-phase).[24] The 3 subtypes of the A-phase correspond to different levels of neurophysiological activation[24]:

> Subtype A1: A-phase with synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or delta bursts in the other NREM stages) associated with mild or trivial polysomnographic variations.

Subtype A2: A-phase with desynchronized EEG patterns preceded by or mixed with slow-voltage waves (K-complexes with alpha and beta activities, K-alpha, arousals with slow-wave synchronization).
Subtype A3: A-phase with desynchronized EEG patterns alone or exceeding 2/3 of the phase length.

We speculate that arousals with slow-wave synchronization[24] in subtype A2 may be a superset of PAHs for 2 reasons. First, the duration A-phase was defined from 2 to 60 seconds,[24] and in this study, PAH duration was defined as 5 seconds or more, so that arousals with slow-wave synchronization may include those shorter than PAH. We also evaluated the maximum duration for a single PAH and found that the duration was 40 seconds. Thus, all PAH durations were included in the A-phase duration of 2–60 seconds.[24] Second, PAH is a delta burst that occurs after arousal, whereas arousals with slow-wave synchronization do not specify the arousal and slow-wave locations. Based on the above, PAH might compose subtype A2 owing to the arousal with slow-wave synchronization.

The PAH function is still unclear, but there is a plausible possibility that it may contribute to the maintenance of NREM sleep after arousal. Since PAH abruptly appeared even in stage N1, its delta burst may differ from slow-waves in SWS. We hypothesize that PAH may have a sleep maintenance function and may be an antiarousal response. It is consistent with the notion from Guilleminault,[45] who referred to the delta burst after arousal as the "defensive delta" and indicated that these delta bursts signified the brain's attempt to stay asleep against arousal. From the viewpoint of antiarousal response in other sleep indices, one of the slow-wave forms as with PAH, the K-complex may have a function of arousal suppression and sleep maintenance.[46] For a K-complex generation, universal and quasi-synchronization across widespread cortical sites occurred.[47] Cortical synchronization is indicative of decreased levels of cortical arousal and a deeper stage of NREM sleep.[48] Thus, PAH may be much more likely to occur to suppress cortical arousal. However, this study could not directly clarify the function of PAH.

In addition, we should consider how PAH would appear in patients with arousal disorders. We speculate that PAH would increase in patients with arousal disorders. The first reason is that PAH might be affected by process S in the current study and SWS has been increased in arousal disorders.[34] The second reason is that PAH correlated with N3 arousal in the present study, and patients with arousal disorders are known to have increased N3 arousals.[9,33] We need further studies to assess how PAH would change in patients with arousal disorder.

Furthermore, it is unknown how PAH would appear in patients with epilepsy. Epileptic seizures and interictal discharges could induce sleep fragmentation and change in sleep architecture, including more significant arousals.[49] Since PAH positively correlated with arousals in this study, we speculate that PAH might also increase in epilepsy patients with frequent arousals. However, it remains unclear whether the arousal induced by epileptic discharge interruption during sleep would be the same as normal arousal in healthy adults. Future studies are needed to clarify how PAH would appear in patients with epilepsy.

Finally, we note the limitations of this study. We evaluated only young participants. Future studies will be needed to investigate PAH in a broad spectrum of ages in children and older adults. We clarify that PAH might be affected by process S and speculate that older adults would have less or no PAH than younger adults because the SWS percentage, which is the marker of process S[11,12] of the participants, dropped with aging.[50] The possibility of the first-night effect[50] in a maximum of 20 participants could be a limitation. In the future, we will investigate the effect of first-night effect on PAH by examining order effects.

In conclusion, we found that the prevalence of PAH in healthy young participants was relatively high. Since PAH increases with early sleep, it may be affected by sleep homeostasis. Because it occurred only in NREM sleep and correlated with the arousal increment, it may function to suppress cortical arousal in NREM sleep.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
EEG, electroencephalography
HSD, hypersynchronous delta activity
NREM, non-rapid eye movement
PAH, postarousal hypersynchrony
PSG, polysomnography
REM, rapid eye movement
SWA, slow-wave activity
SWS, slow-wave sleep

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